Attorney Docket No.: 5/891-1-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No.	: 5,216,167	Appln. No.:	07/495,820
Issued	: June 1, 1993	Filed:	March 19, 1990
Applicant	: Dr. Karl Thomae GmbH.		
For	: PHENYLACETIC ACID BENZYLAMIDES		

February 19, 1998

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATION OF DUPLICATE COPY OF APPLICATION PAPERS FOR PATENT TERM EXTENSION

Sir:

The undersigned hereby certifies that the attached papers are a true, duplicate copy of the original application papers for patent term extension for the above-captioned patent.

Respectfully submitted,

Mary-Ellen M. Devlin
Registration No. 27,928

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, CT 06877
Fax No.: (203)791-6183

Attorney Docket No. 5/891-1-C1 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 5,216,167
Issued: June 1, 1993
Applicant: Dr. Karl Thomae GmbH
Application: 07/495,820
Filed: March 19, 1990
For: Phenylacetic Acid Benzylamides
Date: February 19, 1998

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

PATENT TERM EXTENSION APPLICATION
FOR U.S. PATENT No. 5,216,167 PURSUANT TO 35 U.S.C. § 156

Sir:

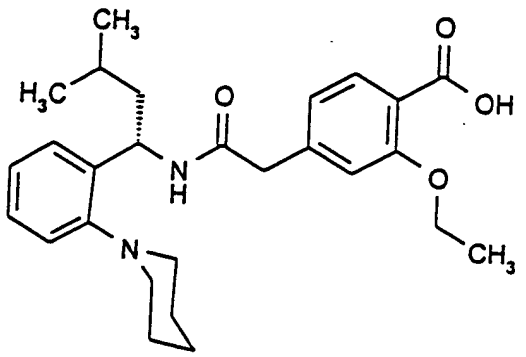
In accordance with 35 U.S.C. § 156 and 37 C.F.R. 1.710 et seq., Applicant hereby applies to the Commissioner for an extension of the patent term for U.S. Patent No. 5,216,167 which discloses and claims the recently approved drug product PRANDIN™ (repaglinide) which has been approved for the treatment of Type 2 diabetes. This application is submitted by the owner of record of the subject patent (Dr. Karl Thomae GmbH) and fully complies with 35 U.S.C. § 156 and 37 C.F.R. 1.710 et seq. which delineate the requirements for the application for extension of patent term.

WRITTEN APPLICATION PURSUANT TO 37 C.F.R. § 1.740(a)

(1) Complete Identification of the Approved Product

The approved drug product that is the basis for this extension request will be sold under the trademark PRANDIN™ and has the generic (international nonproprietary) name "repaglinide." It is disclosed and claimed in U.S. Patent No. 5,216,167. A chemical name

for this approved drug product is (S)-(+)-2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)-phenyl]butyl]amino]-2-oxoethyl]benzoic acid. The chemical structure of this compound is:



Repaglinide is a white to off-white powder with molecular formula $C_{27}H_{36}N_2O_4$ and a molecular weight of 452.6. The remaining physical and chemical properties and descriptors are provided in the FDA approved text for the package insert attached hereto at **Tab 1**.

(2) Complete Identification of the Federal Statute

The Federal Statute under which the applicable regulatory review period occurred was 21 U.S.C. § 355, the provision which regulates the introduction of new drugs into commerce in the United States under the Federal Food, Drug and Cosmetic Act.

(3) Identification of the Date on Which the Product Received Permission for Commercial Marketing or Use

The date that marketing approval was given for the above-identified drug product pursuant to 21 U.S.C. § 355 was December 22, 1997 as shown in the copy of the Approval Letter attached hereto at **Tab 2**.

(4) Identification of Each Active Ingredient in the Drug Product

Applicant hereby asserts that the active ingredient, repaglinide as identified above, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) The Statement that Application Is Being Submitted Within the Sixty-Day Period

Applicant states and asserts that this application for patent term extension is being submitted within the sixty-day period permitted for submission pursuant to § 1.720(f). The product first received permission for commercial marketing or use on **December 22, 1997**. Applicant must submit the patent term application within a sixty-day period beginning on the date that the product first received permission for commercial marketing or use. Accordingly, the last day on which this application can be submitted is **February 20, 1998**. This application is being submitted via Express Mail (# M B230566358) on February 19, 1998, i.e., prior to the expiration of the sixty-day period.

(6) Identification of the Patent for Which an Extension Is Sought

As stated above, the patent for which an extension is being sought is U.S. Patent No. 5,216,167 ("the '167 patent") which issued on June 1, 1993 in the name of Grell et al. Pursuant to 35 U.S.C. § 154(c)(1), the '167 patent has an expiration date of October 10, 2006 (the portion of the term of this patent subsequent to October 10, 2006 has been disclaimed).

A reissue application based upon the '167 patent has also been filed with the United States Patent and Trademark Office ("Patent Office"). Presently, Applicant intends to explore whether or not it is appropriate to disclaim the portion of the term of the '167 patent extending beyond commonly owned U.S. Patent No. 4,863,724. Applicant will advise the Patent Office of the status of this reissue application and any subsequent change as to the expiration date of the '167 patent which may or may not result from the reissue application.

Applicant asserts that it is the Assignee of the entire right, title and interest in the '167 patent by virtue of an assignment from the inventors. This assignment was recorded in the Patent Office on February 1, 1993 at Reel 6404, Frame 0637 and on December 20, 1993 at Reel 6811, Frame 0584.

(7) Copy of Patent

A copy of the '167 patent including the entire specification, claims and drawings is attached hereto at **Tab 3**.

(8) Copy of Disclaimer, Certificate of Correction, Receipt of Maintenance Fee Payment or Reexamination Certificate

Attached hereto at **Tab 4** is a copy of the terminal disclaimer filed with the Patent Office. Also attached at **Tab 4** is a copy of the receipt of maintenance fee payment for the '167 patent.

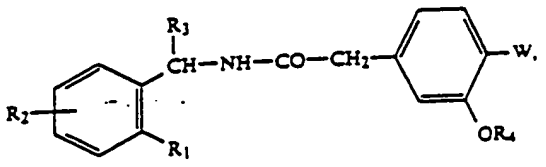
Applicant wishes to note that a Request for a Certificate of Correction has been filed in connection with the '167 patent. This Request has been filed, *inter alia*, to correct an error concerning the filing date that appears on the face of the patent. Applicant will advise the Patent Office of the status of this Request.

Further, as mentioned in paragraph 6 above, a reissue application which may affect the term of the '167 patent is pending. Applicant will advise the Patent Office if there is any change as to the expiration date of the '167 patent.

(9) Statement that the Patent Claims the Approved Product with Showing

Applicant hereby asserts that the '167 patent claims the approved product and a pharmaceutical composition containing the product. The listing of appropriate patent claims which cover the product and the pharmaceutical composition containing the product is as follows:

Claim 1 is directed to a compound of formula (I):



(I)

wherein

R_1 represents an unbranched alkyleneimino group with 4 to 6 carbon atoms optionally mono-or di-(alkyl of 1 to 3 carbon atoms)-substituted;

R_2 represents a hydrogen or halogen atom or a methyl or methoxy group;

R_3 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by a hydroxy, alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain from 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 or 3 carbon atoms and the cycloalkyl part can contain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms;

R_4 represents a hydrogen atom, a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxy, alkoxycarbonyl, cyanomethyl, 2-cyanoethyl, 2-cyanoethenyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, alkoxycarbonylmethyl, 2-alkoxycarbonylethyl or 2-alkoxycarbonylethenyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group; and

when R_3 is other than hydrogen and/or the radical R_1 contains an optically active carbon atom, the enantiomers and the diastereomers thereof or their mixtures; when W is carboxy, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position.

Claim 1 covers repaglinide, the approved drug product, when R_1 is an unbranched, unsubstituted alkylenenimino group with 4 to 6 carbon atoms; R_2 is hydrogen; R_3 is an alkyl group with 1 to 7 carbon atoms; R_4 is an ethyl group; and W is a carboxy group.

Claim 2 is directed to a compound of claim 1, wherein

R_1 represents a pyrrolidino, piperidino, 4-methyl-piperidino, 3-methyl-piperidino, 3,3-dimethyl-piperidino, 3,5-dimethyl-piperidino or hexamethyleneimino group;

R_2 represents a hydrogen, fluorine or chlorine atom;

R_3 represents a hydrogen atom, an alkyl group with 1 to 6 carbon atoms, a phenyl, methyl-phenyl, chloro-phenyl, methoxy-phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, tetrahydrofuran-2-yl-methyl, tetrahydropyran-2-yl-methyl, propargyl, hydroxymethyl, ethoxymethyl, acetoxymethyl, propionyloxymethyl, carboxy, methoxycarbonyl, ethyoxycarbonyl or propoxycarbonyl group or an alkenyl group with 3 or 4 carbon atoms;

R_4 represents a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxy, benzyloxycarbonyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, cyanomethyl, 2-carboxyethyl, 2-ethoxycarbonylethyl, 2-cyano-ethyl, 2-carboxyethenyl, 2-ethoxycarbonyl-ethenyl or 2-cyano-ethenyl group or an alkoxycarbonyl group with 1 to 4 carbon atoms in the alkoxy part; and

when R_3 is other than hydrogen and/or R_1 represents the 3-methyl-piperidino group, the enantiomers and the diastereomers thereof or their mixtures; when W is carboxy, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position.

Claim 2 encompasses the approved product when R_1 is a piperidino group; R_2 is hydrogen; R_3 is an alkyl group with 1 to 6 carbon atoms; R_4 is an ethyl group; and W is a carboxy group.

Claim 3 is directed to a compound of claim 1 wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 1 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, a tetrahydropyran-2-yl-methyl, cyclopropylmethyl, or cyclohexyl-methyl group;

R_4 represents a methyl, ethyl or allyl group; and

W represents a carboxy, methoxycarbonyl, ethoxycarbonyl or cyanomethyl group; and

the enantiomers thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

Claim 3 encompasses the approved product when R_3 is an alkyl group with 1 to 6 carbon atoms, R_4 is an ethyl group and W is a carboxy group.

Claim 4 is directed to a compound of claim 1 wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 3 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, cyclopropylmethyl, or cyclohexylmethyl group;

R_4 represents a methyl or ethyl group; and

W represents a carboxy group; and

the enantiomers thereof or their mixtures; a non-toxic salt thereof formed with inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

Claim 4 encompasses the approved product when R_3 is an alkyl group with 4 carbon atoms, and R_4 is an ethyl group.

Claim 5 is directed to a compound of claim 1 wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 3 to 6 carbon atoms, a 2-methyl-1-propen-1-yl, cyclopropylmethyl, or cyclohexylmethyl group;

R_4 represents a methyl or ethyl group; and

W represents a carboxy group; and

the enantiomers thereof or their mixtures; a non-toxic salt thereof formed with inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

Claim 5 encompasses the approved product when R_3 is an alkyl group with 3 carbon atoms, and R_4 is an ethyl group.

Claim 6 is directed to a compound of claim 5, wherein

R_3 represents an n-propyl, n-butyl, isobutyl, sec.butyl, n-pentyl, 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group;

the enantiomers thereof or their mixtures; a non-toxic salt thereof formed with inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

Claim 6 encompasses the approved product when R_3 is an isobutyl group.

Claim 7 is directed to a compound of claim 5, wherein

R_3 represents an n-propyl, n-butyl, isobutyl, sec.butyl or n-pentyl group; and

the enantiomers thereof or their mixtures; a non-toxic salt thereof formed with inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

Claim 7 encompasses the approved product when R_3 is an isobutyl group.

Claim 9 is directed to a compound of claim 5, which is 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoic acid; the enantiomers thereof or their mixtures; a non-toxic salt thereof formed with inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function. Claim 9 specifically encompasses repaglinide which is the (S)-enantiomer of the compound.

Claim 14 is directed to the (S)-enantiomer of a compound as claimed in any of claims 1-13; when W is carboxy, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position. Claim 14 specifically encompasses the approved product.

Claim 15 is directed to a hypoglycemic pharmaceutical composition consisting essentially of an inert pharmaceutical carrier and an effective hypoglycemic amount of a compound of claim 1. Claim 15 covers the pharmaceutical composition containing effective amounts of the approved drug product.

(10) Statement on Relevant Dates to Enable Determination of the Applicable Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) The investigational new drug (IND) number and the effective date of the IND application:

IND 39,012 effective date **April 3, 1992**;

(b) The date on which U.S. Patent No. 5,216,167 issued:

June 1, 1993;

(c) The new drug application (NDA) number and the date on which the NDA was submitted:

NDA 20-741 submitted **June 27, 1997**;

(d) The date on which the NDA was approved:

December 22, 1997.

(11) A Brief Description of the Significant Activities Undertaken by Applicant

The significant activities undertaken by Novo Nordisk A/S, the exclusive licensee, during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities are described in the IND chronology at **Tab 5** and the NDA chronology at **Tab 6** attached hereto.

As evidenced by the summary of significant activities in the two regulatory chronologies, Applicant asserts that the exclusive licensee, Novo Nordisk A/S, pursued drug product approval for repaglinide with due diligence throughout the regulatory review period.

(12) Statement Regarding Eligibility for Extension

Applicant asserts that U.S. Patent No. 5,216,167 covering the approved drug product PRANDIN™ (repaglinide) is eligible for patent term extension.

Applicant hereby asserts that:

(a) U.S. Patent No. 5,216,167 has not expired before the filing of the application for extension;

(b) the term of the above-identified patent has never been extended under 35 U.S.C. § 156(e)(1);

(c) the application for extension is being timely submitted by the owner of record of the above-identified patent through its attorneys;

(d) the approved drug product has been subject to a regulatory review period before its commercial marketing or use; and

(e) the permission for the commercial marketing or use of the approved product after the regulatory review period is the first such permitted commercial marketing or use of the product under the provision of law under which the regulatory period occurred.

Applicant respectfully submits that it is entitled to an extension of **922 days** which was calculated as follows:

Pursuant to 35 U.S.C. § 156(c), the term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued. Pursuant to 35 U.S.C. § 156(g)(6)(A), the period of extension determined on the basis of the regulatory review period may not exceed five years.

The term "regulatory review period" is defined in 35 U.S.C. § 156(g)(1)(B)(i) and (ii) as follows:

(i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351, 505, or 507, and

(ii) the period beginning on the date the application was initially submitted for the approved drug product under section 351, subsection (b) of section 505, or section 507 and ending on the date such application was approved under such section.

For PRANDIN™ (repaglinide), the regulatory review period is the sum of:

(i) **April 3, 1992** to **June 27, 1997**, less the period of time prior to patent issuance (**June 1, 1993**), or 1487 days, and

(ii) **June 27, 1997** to **December 22, 1997**, or 178 days.

35 U.S.C. § 156(c)(1) requires that the regulatory review period be reduced by any period during which the applicant did not act with due diligence. In this case, Applicant asserts that the regulatory review period should not be reduced for lack of diligence. In addition, 35 U.S.C. § 156(c)(2) provides that the period of extension shall include only one-half of the time described in Section (g)(1)(B)(i).

The revised regulatory review period would thus equal (1/2)(1487) + 178 = **922 days** or **2 years plus 192 days**.

35 U.S.C. § 156(c)(3) further provides that if the period remaining in the term of the patent after the date of the approval of the approved product when added to the revised regulatory review period exceeds 14 years, the period of extension shall be reduced so that the total of both such periods does not exceed 14 years.

The term of the patent remaining after **December 22, 1997** (the NDA approval date) is calculated as follows:

Patent expiration date (due to terminal disclaimer) = **October 10, 2006**

December 22, 1997 to October 10, 2006 = 3,214 days or **8 years plus 292 days**

The extended term of the subject patent after approval if the entire revised regulatory period is added to the patent term remaining after approval is calculated as follows:

8 years plus 292 days + 2 years plus 192 days = **11 years plus 119 days**

Accordingly, since the sum of the remaining patent term after approval and the requested extension term does not exceed 14 years, Applicant is entitled to the full extension requested, i.e., **922 days**. The patent expiration date with this extension would be **April 19, 2009.**

(13) Duty to Disclose

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

Applicant wishes to note that it is concurrently filing herewith a patent term extension application for commonly owned U.S. Patent No. 5,312,924. Applicant provisionally elects the '167 patent for patent term extension at this time. However, upon written notice from

the Patent Office as to the sufficiency of each patent term extension application, Applicant will confirm its election.

Further, in an abundance of caution, Applicant wishes to note the existence of U.S. Patent Nos. 4,863,724 and 4,873,080, each of which is commonly owned by Applicant. Generally, these patents disclose pharmaceutical compositions and methods of preparing pharmaceutical compositions that can be used to formulate repaglinide. Applicant is not filing patent term extension applications for these patents.

(14) The Prescribed Fee for Acting on this Application

Applicant hereby authorizes withdrawal from Deposit Account No. 02-2955 the appropriate fee of $1,120.00 for receiving and acting upon the application for extension pursuant to 37 C.F.R. § 1.20(j)(1). Applicant also authorizes any additional fee as a result of any fee change from the above deposit account.

(15) Name, Address and Telephone Number of Person To Whom Inquiries Should Be Directed

The name, address and telephone number of the person to whom inquiries and correspondence relating to this application is the undersigned attorney listed below:

Mary-Ellen M. Devlin
Registration No. 27,928
Attorney for Applicant
BOEHRINGER INGELHEIM
PHARMACEUTICALS, INC.
900 Ridgebury Rd./P.O. Box 368
Ridgefield, CT 06877-0368
Phone (203) 798-4866
Fax (203) 791-6183

(16) Certified Duplicates of Application Papers

Four certified duplicates of these application papers are provided herewith.

(17) Declaration Pursuant to 37 C.F.R. § 1.740(b)

With respect to the application presented herewith for the extension of the term of U.S. Patent No. 5,216,167, Applicant hereby declares that the person signing below and making this declaration is:

(a) A patent attorney authorized to practice before the Patent and Trademark Office who has general authority to act on behalf of the owner of the above-identified patent in patent matters;

(b) Has reviewed and understands the contents of this application for patent term extension of U.S. Patent No. 5,216,167 being submitted pursuant to 37 C.F.R. § 1.740;

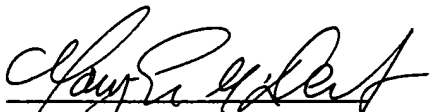
(c) Believes the patent is subject to extension pursuant to 37 C.F.R. § 1.710;

(d) Believes an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(e) Believes the patent for which extension is being sought meets the conditions for extension as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of this application.

Respectfully submitted,



DATE: February 19, 1998
Express Mail
No. M B230566358

Mary-Ellen M. Devlin
Registration No. 27,928
Attorney for Applicant
BOEHRINGER INGELHEIM
PHARMACEUTICALS, INC.
900 Ridgebury Rd./P.O. Box 368
Ridgefield, CT 06877-0368
Phone (203) 798-4866
Fax (203) 791-6183

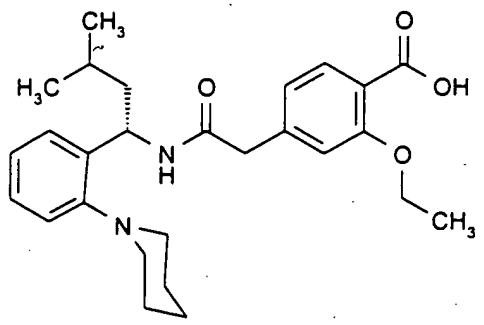
PRANDIN™

(repaglinide) Tablets (0.5, 1, and 2 mg)

DESCRIPTION

PRANDIN™ (repaglinide) is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

The structural formula is as shown below:



Repaglinide is a white to off-white powder with molecular formula C_{27} H_{36} N_2 O_4 and a molecular weight of 452.6. PRANDIN™ tablets contain 0.5 mg, 1 mg, or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, polacrilin potassium, povidone, glycerol (85%), magnesium stearate, meglumine, and poloxamer. The 1 mg and 2 mg tablets contain iron oxides (yellow or red, respectively) as coloring agents.

CLINICAL PHARMACOLOGY

Mechanism of Action

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

Pharmacokinetics

Absorption: After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean T_{MAX} was not changed, but the mean C_{MAX} and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution: After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state (V_{ss}) was 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 3A4, has been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.

Excretion: Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

Pharmacokinetic parameters: The pharmacokinetic parameters of repaglinide obtained from a single-dose, crossover study in healthy subjects and from a multiple- dose, parallel, dose-proportionality (0.5, 1, 2 and 4 mg) study in patients with type 2 diabetes are summarized below:

Parameter	Patients with type 2 diabetes[a]
Dose 0.5 mg 1 mg 2 mg 4 mg	$AUC_{0\text{-}24\ hr}$ Mean ±SD (ng/mL*hr): 68.9 ±154.4 125.8 ±129.8 152.4 ±89.6 447.4 ±211.3
Dose 0.5 mg 1 mg 2 mg 4 mg	$C_{max0\text{-}5\ hr}$ Mean ±SD (ng/mL): 9.8 ±10.2 18.3 ±9.1 26.0 ±13.0 65.8 ±30.1
Dose 0.5 - 4 mg	$T_{max0\text{-}5\ hr}$ Means (SD) 1.0 - 1.4 (0.3 - 0.5) hr
Dose 0.5 - 4 mg	$T_{½}$ Mean (Ind Range) 1.0 - 1.4 (0.4 - 8.0) hr
Parameter	Healthy Subjects
CL based on i.v.	38± 16 L/hr
V_{ss} based on i.v.	31± 12 L
AbsBio	56± 9 %

a: dosed preprandially with three meals

CL = Total body clearance
V_{ss} = Volume of distribution at steady state
AbsBio = Absolute bioavailability

These data indicate that repaglinide did not accumulate in serum. Clearance of oral repaglinide did not change over the 0.5 - 4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of exposure: Repaglinide AUC after multiple doses of 0.25 to 4 mg with each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over the therapeutic dose range included 69 to 1005 ng/mL*hr, but AUC exposure up to 5417 ng/mL*hr was reached in dose escalation studies without apparent adverse consequences.

Special populations:

Geriatric. Healthy volunteers were treated with a regimen of 2 mg taken before each of 3 meals. There were no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and a comparably sized group of patients ≥65 years of age. (See **PRECAUTIONS, Geriatric Use**)

Pediatric. No studies have been performed in pediatric patients.

Gender. A comparison of pharmacokinetics in males and females showed the AUC over the 0.5 mg to 4 mg dose range to be 15% to 70% higher in females with type 2 diabetes. This difference was not reflected in the frequency of hypoglycemic episodes (male: 16%; female: 17%) or other adverse events. With respect to gender, no change in general dosage recommendation is indicated since dosage for each patient should be individualized to achieve optimal clinical response.

Race. No pharmacokinetic studies to assess the effects of race have been performed, but in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect was comparable between Caucasians (n=297) and African-Americans (n=33). In a U.S. dose-response study, there was no apparent difference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

Renal insufficiency.

Single-dose and steady-state pharmacokinetics of repaglinide were evaluated in patients with various degrees of renal impairment. Measures of AUC and C_{max} after multiple dosing of 2 mg repaglinide were found to be higher in three groups of patients with reduced renal function ($AUC_{mild/moderate\ impairment}$: 90.8 ng/mL*hr to $AUC_{severe\ impairment}$: 137.7 ng/mL*hr versus $AUC_{healthy}$:29.1 ng/mL*hr; $C_{max,\ mild/moderate\ impairment}$: 46.7 ng/mL to $C_{max,\ severe\ impairment}$: 44.0 ng/mL versus $C_{max,\ healthy}$:20.6 ng/mL). Repaglinide AUC is only weakly correlated to creatinine clearance. Initial dosage adjustment does not appear to be necessary, but **subsequent increases in PRANDIN™ should be made carefully in patients with type 2 diabetes who have renal function impairment or renal failure requiring hemodialysis**.

Hepatic insufficiency.

A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91.6 ng/mL*hr;

$AUC_{CLD\ patients}$: 368.9 ng/mL*hr; $C_{max,\ healthy}$: 46.7 ng/mL: $C_{max,\ CLD\ patients}$: 105.4 ng/mL.). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, **PRANDIN™ should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.**

Clinical Trials

A four-week, double-blind, placebo-controlled dose-response trial was conducted in 138 patients with type 2 diabetes using doses ranging from 0.25 to 4 mg taken with each of three meals. PRANDIN™ therapy resulted in dose- proportional glucose-lowering over the full dose range. Plasma insulin levels increased after meals and reverted toward baseline before the next meal. Most of the fasting blood glucose-lowering effect was demonstrated within 1-2 weeks.

In a double-blind, placebo-controlled, 3-month dose titration study, PRANDIN™ or placebo doses for each patient were increased weekly from 0.25 mg through 0.5, 1, and 2 mg, to a maximum of 4 mg, until a fasting plasma glucose (FPG) level <160 mg/dL was achieved or the maximum dose reached. The dose that achieved the targeted control or the maximum dose was continued to end of study . FPG and 2-hour post-prandial glucose (PPG)

increased in patients receiving placebo and decreased in patients treated with repaglinide. Differences between the repaglinide- and placebo-treated groups were -61 mg/dL (FPG) and -104 mg/dL (PPG). The between-group change in $HbA1_c$, which reflects long-term glycemic control, was 1.7% units.

Prandin vs. Placebo Treatment: Mean FPG, PPG , and $HbA1_c$ Changes from baseline after 3 months of treatment:

	FPG (mg/dL)		PPG (mg/dL)		$HbA1_c$ (%)	
	PL	R	PL	R	PL	R
Baseline	215.3	220.2	245.2	261.7	8.1	8.5
Change from Baseline (at last visit)	30.3	-31.0*	56.5	-47.6*	1.1	-0.6*

FPG = fasting plasma glucose PPG = post-prandial glucose

PL = placebo (N=33) R = repaglinide (N=66)

* $p < 0.05$ for between group difference

Another double-blind, placebo-controlled trial was carried out in 362 patients treated for 24 weeks. The efficacy of 1 and 4 mg preprandial doses was demonstrated by lowering of fasting blood glucose and by HbA1c at the end of the study. $HbA1_c$ for the PRANDIN™-treated groups (1 and 4 mg groups combined) at the end of the study was decreased compared to the placebo-treated group in previously naïve patients and in patients

previously treated with oral hypoglycemic agents by 2.1% units and 1.7% units, respectively. In this fixed-dose trial, patients who were naïve to oral hypoglycemic agent therapy and patients in relatively good glycemic control at baseline (HbA1c below 8%) showed greater blood glucose-lowering including a higher frequency of hypoglycemia. Patients who were previously treated and who had baseline HbA1c $\geq$ 8% reported hypoglycemia at the same rate as patients randomized to placebo. There was no average gain in body weight when patients previously treated with oral hypoglycemic agents were switched to PRANDIN™. The average weight gain in patients treated with PRANDIN™ and not previously treated with sulfonylurea drugs was 3.3%.

The dosing of PRANDIN™ relative to meal-related insulin release was studied in three trials including 58 patients. Glycemic control was maintained during a period in which the meal and dosing pattern was varied (2, 3, or 4 meals per day; before meals x 2, 3, or 4) compared with a period of 3 regular meals and 3 doses per day (before meals x 3). It was also shown that PRANDIN™ can be administered at the start of a meal, 15 minutes before, or 30 minutes before the meal with the same blood glucose lowering effect.

PRANDIN™ was compared to other insulin secretagogues in 1-year controlled trials to demonstrate comparability of efficacy and safety. Hypoglycemia was reported in16% of 1228 PRANDIN™ patients, 20% of 417 glyburide patients, and 19% of 81 glipizide patients. Of PRANDIN™ treated patients with symptomatic hypoglycemia, none developed coma or required hospitalization.

PRANDIN™ was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. Combination therapy with PRANDIN™ and metformin resulted in synergistic improvement in glycemic control compared to repaglinide or metformin monotherapy. $HbA1_c$ was improved by 1% unit and FPG decreased by an additional 35 mg/dL.

PRANDIN™ and Metformin Therapy: Mean $HbA1_c$ and FPG Changes from Baseline after 3 Months Treatment

	PRANDIN™	Combination	Metformin
N	28	27	27
$HbA1_c$ (% units)	-0.38	-1.41	-0.33
FPG (mg/dL)	8.8	-39.2	-4.5

INDICATIONS AND USAGE

PRANDIN™ is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.

PRANDIN™ is also indicated for use in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet, and either repaglinide or metformin alone. If glucose control has not been achieved after a suitable trial of combination therapy, consideration should be given to discontinuing these drugs and using insulin. Judgments should be based on regular clinical and laboratory evaluations.

In initiating treatment for patients with type 2 diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral blood glucose-lowering agent or insulin should be considered. Use of PRANDIN™ must be viewed by both the physician and patient as a treatment in addition to diet, and not as a

substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of PRANDIN™.

During maintenance programs, PRANDIN™ should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

The Diabetes Control and Complications Trial (DCCT) demonstrated, in patients with type 1 diabetes, that improved glycemic control, as reflected by $HbA1_c$ and fasting glucose levels, was associated with a reduction in the diabetic complications retinopathy, neuropathy, and nephropathy. In considering the use of PRANDIN™ or other antidiabetic therapies, it should be recognized that controlling the blood glucose in type 2 diabetes has not been established to be effective in preventing the long-term cardiovascular and neural complications of diabetes. It has not been shown that the implications of the DCCT results also apply to patients with type 2 diabetes. Nonetheless, improved glycemic control appears to be an important goal in many patients with non-insulin-dependent disease because it is presumed that the mechanisms by which glucose causes complications is the same in both forms of diabetes.

CONTRAINDICATIONS

PRANDIN™ is contraindicated in patients with:

1. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
2. Type1 diabetes.
3. Known hypersensitivity to the drug or its inactive ingredients.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with type 2 diabetes (NIDDM). The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 (Suppl. 2): 747-830; 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately

2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of repaglinide and of alternative modes of therapy.

Although PRANDIN™ was not included in the UGDP study, it is prudent from a safety standpoint to consider that this warning may also apply to this oral hypoglycemic agent, in view of similarities in mode of action.

PRECAUTIONS

General: Hypoglycemia: All oral blood glucose-lowering drugs are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemia. Elderly, debilitated, or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is

deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

The frequency of hypoglycemia is greater in patients with type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (naive) or whose $HbA1_c$ is less than 8%. PRANDIN™ should be administered with meals to lessen the risk of hypoglycemia.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue PRANDIN™ and administer insulin. The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when the drug is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients

Patients should be informed of the potential risks and advantages of PRANDIN™ and of alternative modes of therapy. They should also be informed about the importance of

adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose and $HbA1_c$.The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to take PRANDIN™before meals (2, 3, or 4 times a day preprandially). Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing these levels towards the normal range. During dose adjustment, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Glycosylated hemoglobin may be especially useful for evaluating long-term glycemic control.

Drug Interactions

In vitro data indicate that repaglinide metabolism may be inhibited by antifungal agents like ketoconazole and miconazole, and antibacterial agents like erythromycin. Drugs that induce the cytochrome P-450 enzyme system 3A4 may increase repaglinide metabolism; such drugs include troglitazone, rifampicin, barbiturates, and carbamazepine. No systematically acquired data are available on increased or decreased plasma levels with 3A4 inhibitors or inducers.

Drug interaction studies performed in healthy volunteers show that PRANDIN™ had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Thus, no dosage adjustment is required for digoxin, theophylline, or warfarin on coadministration of PRANDIN™. Co-administration of cimetidine with PRANDIN™ did not significantly alter the absorption and disposition of repaglinide.

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When these drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or approximately 60 and 125 times clinical exposure, respectively, on a mg/m^2 basis. No evidence of carcinogenicity was found in mice or female rats. In male rats, there was an increased incidence of benign adenomas of the thyroid and liver. The relevance of these findings to humans is unclear. The no-effect doses for these observations in male rats were 30 mg/kg body weight/day for thyroid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m^2 basis.

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro*

chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m^2 basis.

Pregnancy

Pregnancy category C

Teratogenic Effects: Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) clinical exposure (on a mg/m^2 basis) throughout pregnancy. Because animal reproduction studies are not always predictive of human response, PRANDIN™ should be used during pregnancy only if it is clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of PRANDIN™ administration throughout pregnancy or lactation cannot be established.

Nursing Mothers

In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. Cross fostering studies indicated that skeletal changes (see **Nonteratogenic Effects**) could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated *in utero*. Although it is not known whether repaglinide is excreted in human milk some oral agents are known to be excreted by this route. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, a decision should be made as to whether PRANDIN™ should be discontinued in nursing mothers, or if mothers should discontinue nursing. If PRANDIN™ is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

No studies have been performed in pediatric patients.

Geriatric Use

In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related increase in cardiovascular events observed for PRANDIN™ and comparator drugs. There was no increase in frequency or severity of hypoglycemia in older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to PRANDIN™ therapy cannot be ruled out.

ADVERSE REACTIONS

Hypoglycemia: See **Precautions** and

Overdosage Sections.

PRANDIN™ has been administered to 2931 individuals during clinical trials. Approximately 1500 of these individuals with type 2 diabetes have been treated for at least 3 months, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received PRANDIN™ in one of five 1-year, active-controlled trials. The comparator drugs in these 1-year trials were oral sulfonylurea drugs (SU) including glyburide and glipizide. Over one year, 13% of PRANDIN™ patients were discontinued due to adverse events as were 14% of SU patients. The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms (see **PRECAUTIONS**). Mild or moderate hypoglycemia occurred in 16% of PRANDIN™ patients, 20% of glyburide patients, and 19% of glipizide patients.

The table below lists common adverse events for PRANDIN™ patients compared to both placebo (in trials less than 6 months duration) and to glyburide and glipizide in one year trials. The adverse event profile of PRANDIN™ was generally comparable to that for sulfonylurea drugs (SU).

Commonly Reported Adverse Events (% of Patients)*

EVENT	PRANDIN N = 352	PLACEBO N = 108	PRANDIN N = 1228	SU N = 498
	Placebo controlled studies		Active controlled studies	
Metabolic				
Hypoglycemia	31**	7	16	20
Respiratory				
URI	16	8	10	10
Sinusitis	6	2	3	4
Rhinitis	3	3	7	8
Bronchitis	2	1	6	7
Gastrointestinal				
Nausea	5	5	3	2
Diarrhea	5	2	4	6
Constipation	3	2	2	3
Vomiting	3	3	2	1
Dyspepsia	2	2	4	2
Musculoskeletal				
Arthralgia	6	3	3	4
Back Pain	5	4	6	7
Other				
Headache	11	10	9	8
Paresthesia	3	3	2	1
Chest pain	3	1	2	1
Urinary tract infection	2	1	3	3
Tooth disorder	2	0	<1	<1
Allergy	2	0	1	<1

* Events ≥2% for the PRANDIN™ group in the placebo-controlled studies and ≥ events in the placebo group

** See trial description in **CLINICAL PHARMACOLOGY, Clinical Trials**

Cardiovascular events also occur commonly in patients with type 2 diabetes. In one-year comparator trials, the incidence of individual events was not greater than 1% except for chest pain (1.8%) and angina (1.8%). The overall incidence of other cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤1% and not different for PRANDIN™ and the comparator drugs.

The incidence of serious cardiovascular adverse events added together, including ischemia, was slightly higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1-year controlled trials, PRANDIN™ treatment was not associated with excess mortality rates compared to rates observed with other oral hypoglycemic agent therapies.

Summary of Serious Cardiovascular Events (% of total patients with events)

	PRANDIN™	SU*
Total Exposed	1228	498
Serious CV Events	4%	3%
Cardiac Ischemic Events	2%	2%
Deaths due to CV Events	0.1%	0.04%

* glyburide and glipizide

Infrequent adverse events (<1% of patients)

Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, thrombocytopenia, leukopenia, and anaphylactoid reactions (one patient).

OVERDOSAGE

In a clinical trial, patients received increasing doses of PRANDIN™ up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring may continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of type 2 diabetes with PRANDIN™. The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

Short-term administration of PRANDIN™ may be sufficient during periods of transient loss of control in patients usually well controlled on diet.

PRANDIN™ doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

Starting Dose

For patients not previously treated or whose $HbA1_c$ is < 8%, the starting dose should be 0.5 mg. For patients previously treated with blood glucose-lowering drugs and whose $HbA1_c$ is ≥ 8%, the initial dose is 1 or 2 mg with each meal preprandially (see previous paragraph).

Dose Adjustment

Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. The preprandial dose should be doubled up to 4 mg until satisfactory blood glucose response is achieved. At least one week should elapse to assess response after each dose adjustment.

The recommended dose range is 0.5 mg to 4 mg taken with meals. PRANDIN™ may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.

Patient Management

Long-term efficacy should be monitored by measurement of $HbA1_c$ levels approximately every 3 months. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy including hypoglycemia.

Patients Receiving Other Oral Hypoglycemic Agents

When PRANDIN™ is used to replace therapy with other oral hypoglycemic agents, PRANDIN™ may be started on the day after the final dose is given. Patients should then be observed carefully for hypoglycemia due to potential overlapping of drug effects. When

transferred from longer half-life sulfonylurea agents (e.g., chlorpropamide) to repaglinide, close monitoring may be indicated for up to one week or longer.

Combination Therapy

If PRANDIN™ monotherapy does not result in adequate glycemic control, metformin may be added. Or, if metformin therapy does not provide adequate control, PRANDIN™ may be added. The starting dose and dose adjustments for PRANDIN™ combination therapy is the same as for PRANDIN™ monotherapy. The dose of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Appropriate monitoring of FPG and $HbA1_c$ measurements should be used to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure.

HOW SUPPLIED

PRANDIN™ (repaglinide) tablets are supplied as unscored, biconvex tablets available in 0.5 mg (white), 1 mg (yellow) and 2 mg (red) strengths. Tablets are embossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength.

0.5 mg tablets	Bottles of 100	NDC 00169-0081-81
(white)	Bottles of 500	NDC 00169-0081-82
	Bottles of 1000	NDC 00169-0081-83

1 mg tablets	Bottles of 100	NDC 00169-0082-81
(yellow)	Bottles of 500	NDC 00169-0082-82
	Bottles of 1000	NDC 00169-0082-83
2 mg tablets	Bottles of 100	NDC 00169-0084-81
(red)	Bottles of 500	NDC 00169- 0084-82
	Bottles of 1000	NDC 00169-0084-83

Do not store above 25 C (77 F). Protect from moisture. Keep bottles tightly closed.

Dispense in tight containers with safety closures.

Caution

Federal law prohibits dispensing without a prescription.

PRANDIN™ is a trademark of Novo Nordisk A/S.

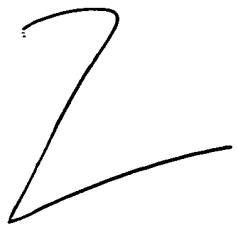
Manufactured in Germany for

Novo Nordisk Pharmaceuticals,Inc.

100 Overlook Center, Suite 200

Princeton, NJ 08540.

1-800-727-6500



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-741

December 22, 1997

Novo Nordisk Pharmaceuticals Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

Dear Dr. Reit:

Please refer to your new drug application dated June 27, 1997, received July 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prandin™ (repaglinide) 0.5 mg, 1 mg, and 2 mg Tablets.

We acknowledge receipt of your submissions dated August 14, 20, 26, and 27, September 2, 8, and 17, October 3, 14, 16, and 23, and December 12, 17, 18, and 22 (fax), 1997. The User Fee goal date for this application is January 1, 1998.

This new drug application provides for the use of Prandin™ Tablets as an adjunct to diet and exercise to lower blood glucose in patients with non-insulin dependent (type II) diabetes mellitus whose hyperglycemia cannot be controlled satisfactorily with diet and exercise alone. It also provides for the use of Prandin™ Tablets in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet, and either repaglinide or metformin alone.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted (fax) on December 22, 1997, and the draft carton and container labeling dated June 27 and October 16, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-741. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become

available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated December 22 (fax), 1997. These commitments are listed below.

1. A long-term, simplified clinical trial to assess further the long-term safety, including the incidence of cardiovascular events, in patients with type 2 diabetes treated with Prandin™, a long acting sulfonylurea drug, and other established therapy.

2. A clinical trial to assess efficacy in patients with type 2 diabetes and renal dysfunction.

3. Normal volunteer studies to document pharmacokinetic drug interactions with statins, estrogen, and calcium channel blockers.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii), we request a status summary of each commitment in your annual report to this application. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth

under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Regulatory Management Officer, at (301) 827-6423.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

3

US005216167A

United States Patent [19]

Grell et al.

[11] Patent Number: 5,216,167

[45] Date of Patent: * Jun. 1, 1993

[54] PHENYLACETIC ACID BENZYLAMIDES

[75] Inventors: Wolfgang Grell; Rudolf Hurnaus, both of Biberach; Gerhart Griss, deceased, late of Biberach, by Elisabeth Griss, executrix; Robert Sauter, Laupheim; Manfred Reiffen, Biberach; Eckhard Rupprecht, Aulendorf-Tannhausen, all of Fed. Rep. of Germany

[73] Assignee: Dr. Karl Thomae GmbH, Biberach an der Riss, Fed. Rep. of Germany

[*] Notice: The portion of the term of this patent subsequent to Oct. 10, 2006 has been disclaimed.

[21] Appl. No.: 495,820

[22] Filed: Jun. 21, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 302,022, Jan. 25, 1989, abandoned, and a continuation-in-part of Ser. No. 878,921, Jun. 26, 1986, abandoned, and a continuation-in-part of Ser. No. 872,706, Jun. 10, 1986, abandoned, which is a continuation-in-part of Ser. No. 684,054, Dec. 10, 1984, abandoned.

[30] Foreign Application Priority Data

Dec. 30, 1983 [DE] Fed. Rep. of Germany 3347565
Jun. 25, 1985 [DE] Fed. Rep. of Germany 3522604
Jul. 1, 1985 [DE] Fed. Rep. of Germany 3523466

[51] Int. Cl.[5] C07D 211/32; C07D 207/08; A61K 31/445; A61K 31/40

[52] U.S. Cl. 546/234; 540/609; 546/214; 548/517; 548/568; 549/414; 549/415; 549/426; 549/427; 549/473; 549/496; 558/414; 564/168; 514/212; 514/326; 514/331; 514/422; 514/429; 514/450; 514/461; 514/522; 514/619

[58] Field of Search 546/234, 214; 514/331; 548/517, 568; 564/168

[56] References Cited

U.S. PATENT DOCUMENTS

4,542,127 9/1985 Hitzel et al. 546/194
4,735,959 4/1988 Grell et al. 546/234

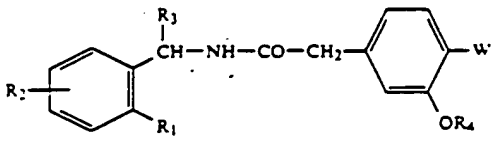
FOREIGN PATENT DOCUMENTS

2091729 8/1982 United Kingdom 546/234

Primary Examiner—Allen J. Robinson
Assistant Examiner—Brian Bembenick
Attorney, Agent, or Firm—D. E. Frankhouser; A. R. Stempel; M-E. M. Timbers

[57] ABSTRACT

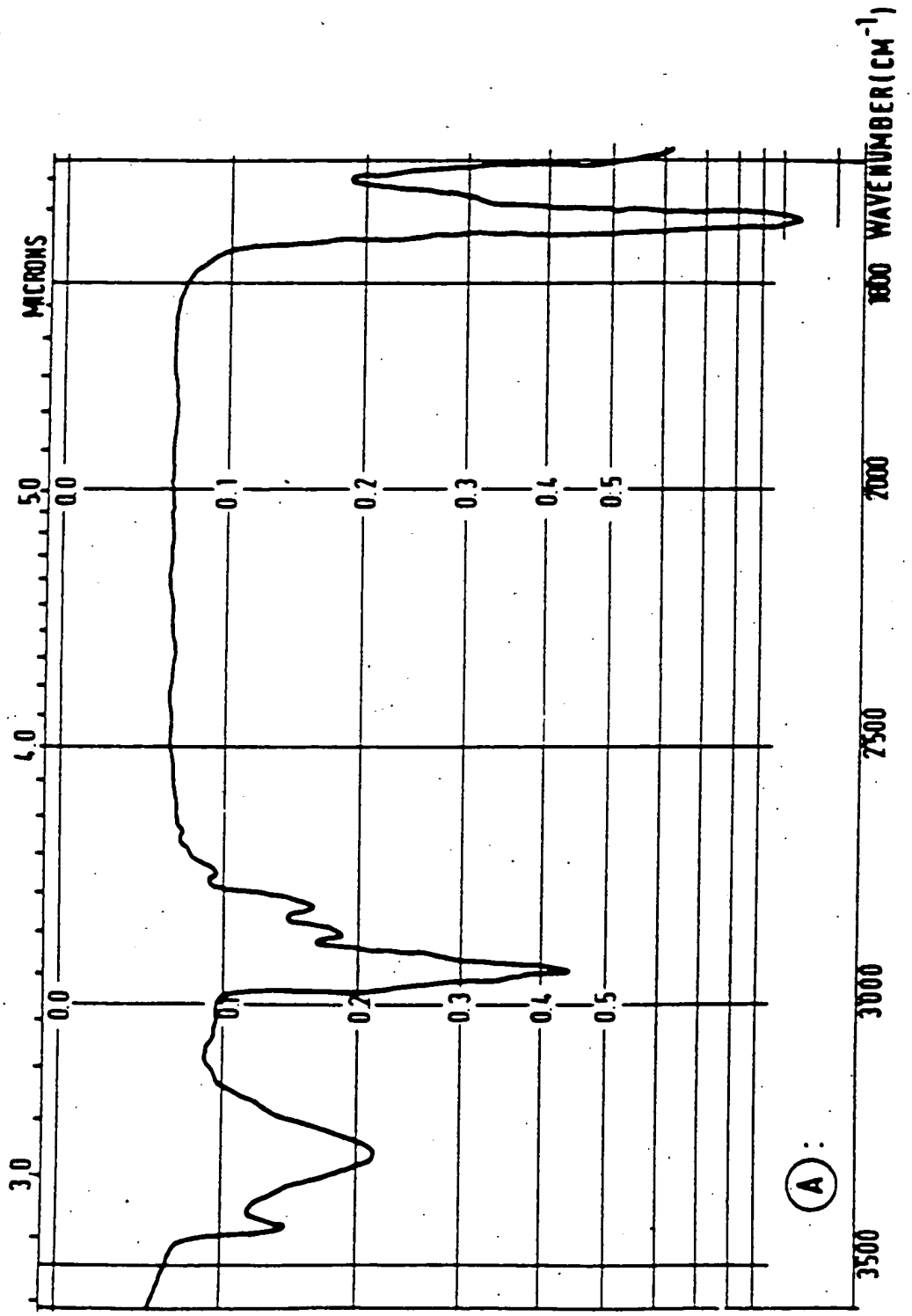
Phenylacetic acid benzylamides having the following general structure



wherein the substituents are defined herein, are disclosed, which compounds are hypoglcemic agents.

15 Claims, 12 Drawing Sheets

FIG. 1 (PART 1)


MICRONS
5.0
4.0
3.0
0.0
0.1
0.2
0.3
0.4
0.5
WAVENUMBER(CM-1)
3500
3000
2500
2000
A

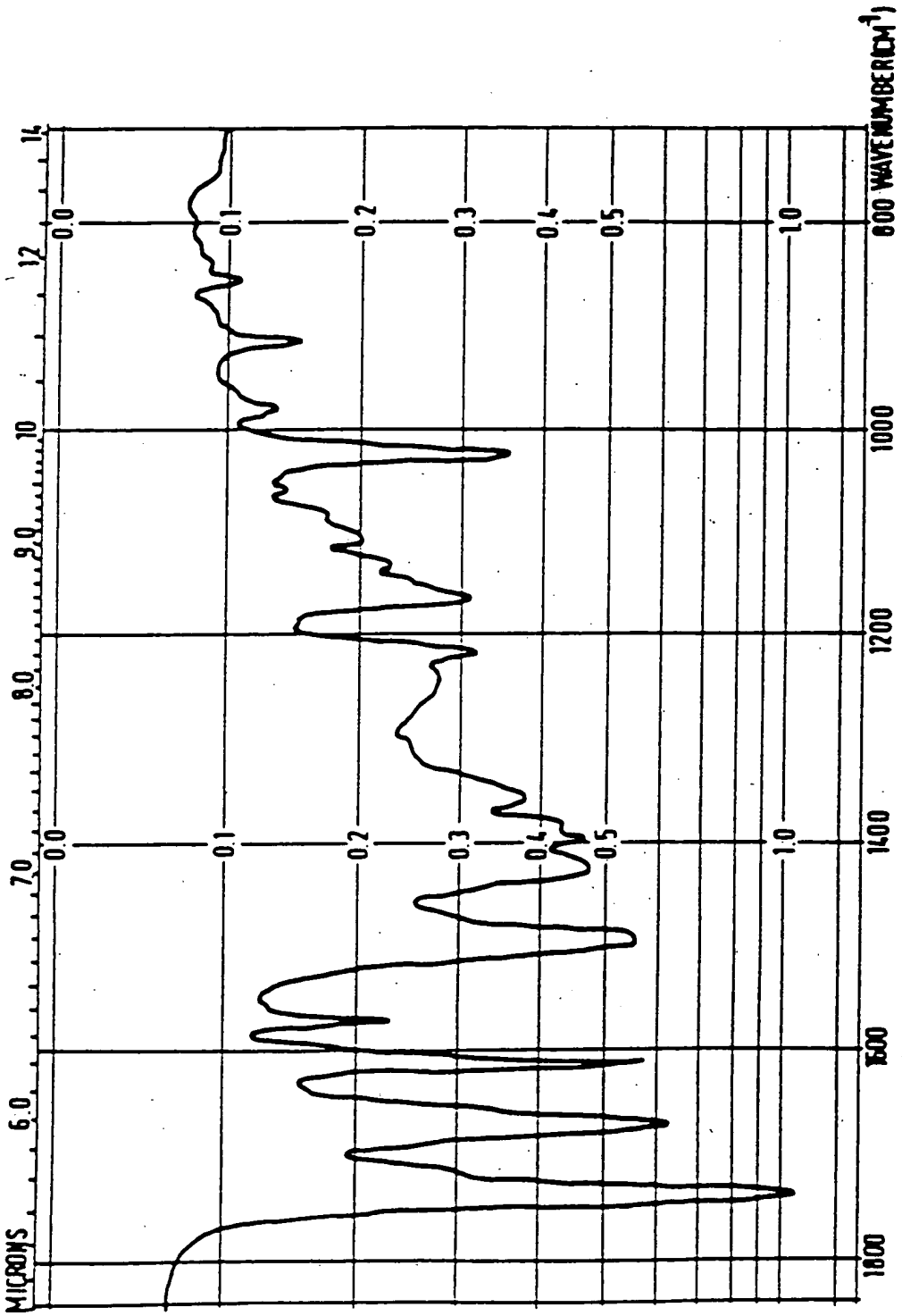

MICRONS
6.0
7.0
8.0
9.0
10
12
14
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1800
1600
1400
1200
1000
800 WAVENUMBER(CM-1)

FIG. 1 (PART 2)

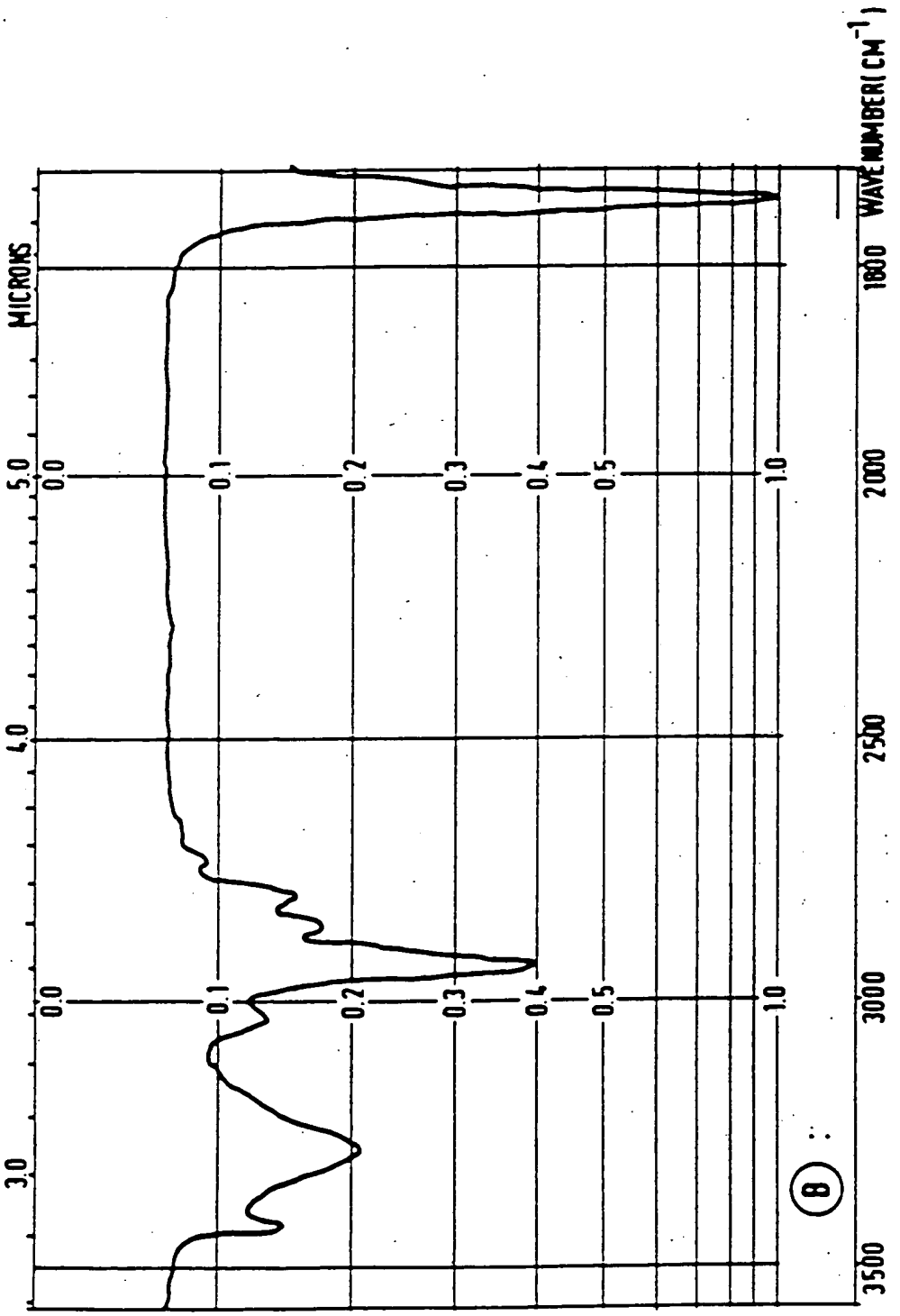

MICRONS
5.0
4.0
3.0
0.0
0.1
0.2
0.3
0.4
0.5
1.0
WAVE NUMBER (CM^{-1})
1800
2000
2500
3000
3500
(B)

FIG. 2 (PART 1)

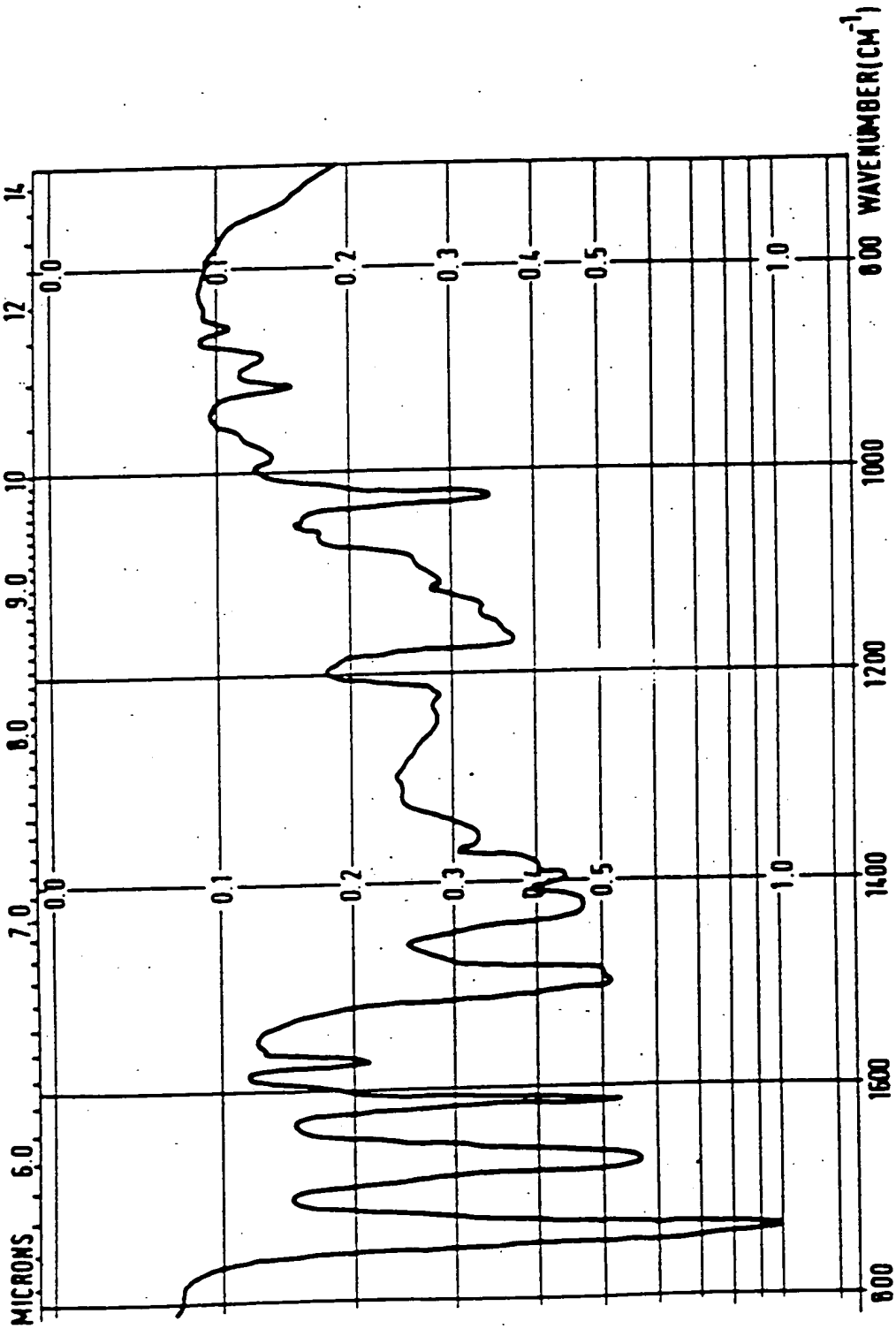

MICRONS
6.0
7.0
8.0
9.0
10
12
14
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1600
1400
1200
1000
800
WAVENUMBER(CM-1)

FIG. 2 (PART 2)

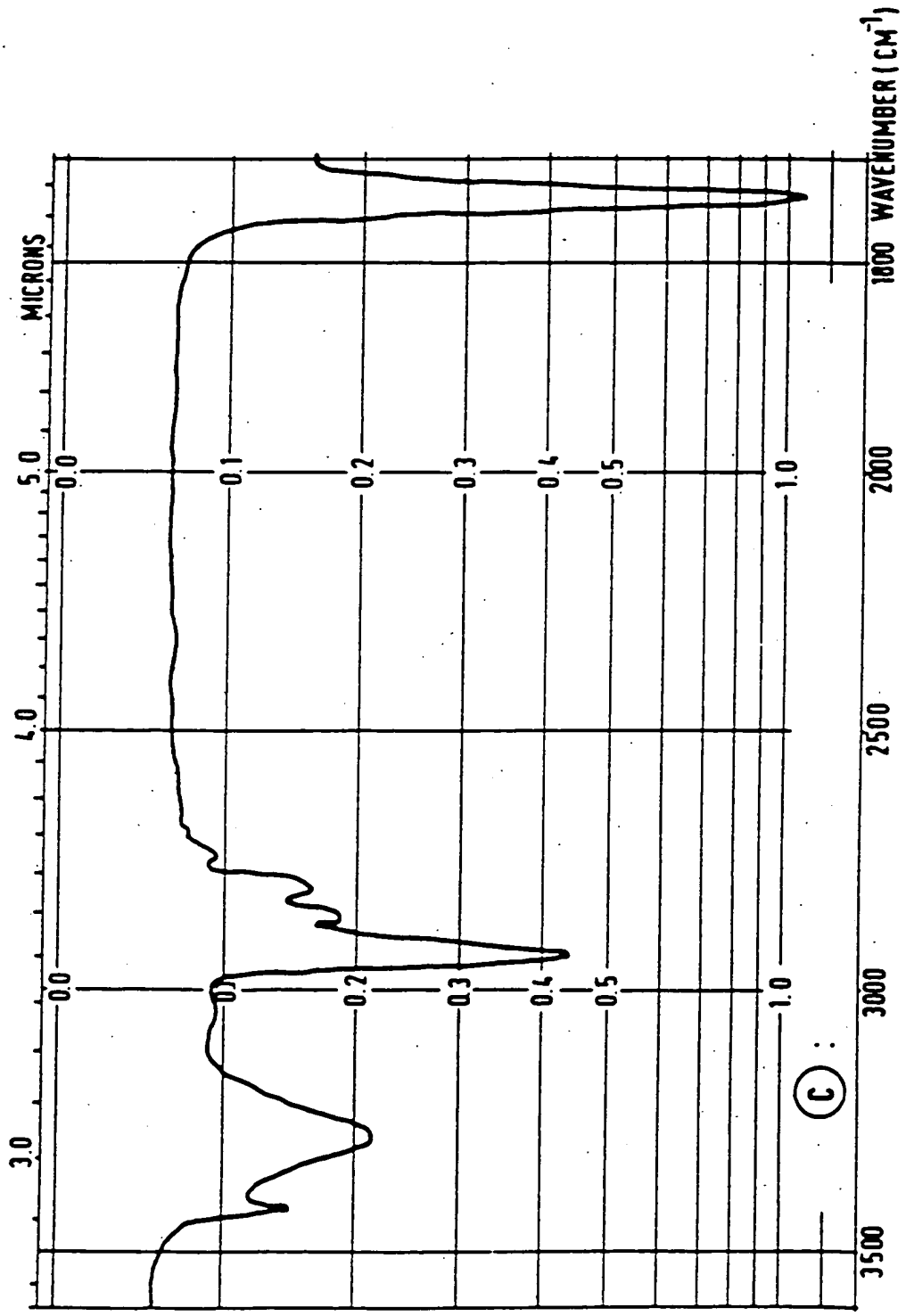

MICRONS
5.0
4.0
3.0
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1000
2000
2500
3000
3500
WAVENUMBER (CM⁻¹)
C :

FIG. 3 (PART 1)

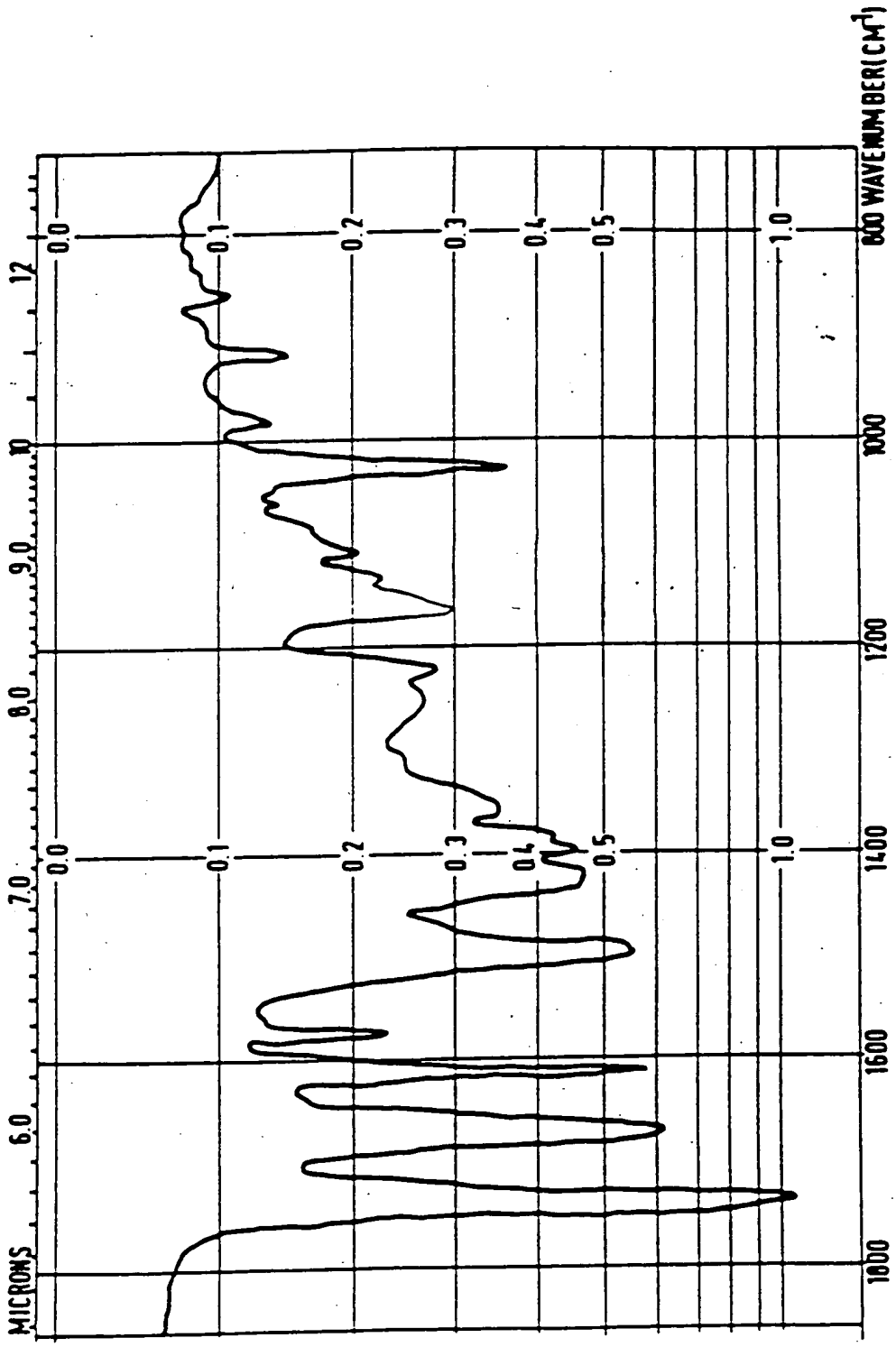

MICRONS
6.0
7.0
8.0
9.0
10
12
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1800
1600
1400
1200
1000
800 WAVENUMBER (CM⁻¹)

FIG. 3 (PART 2)

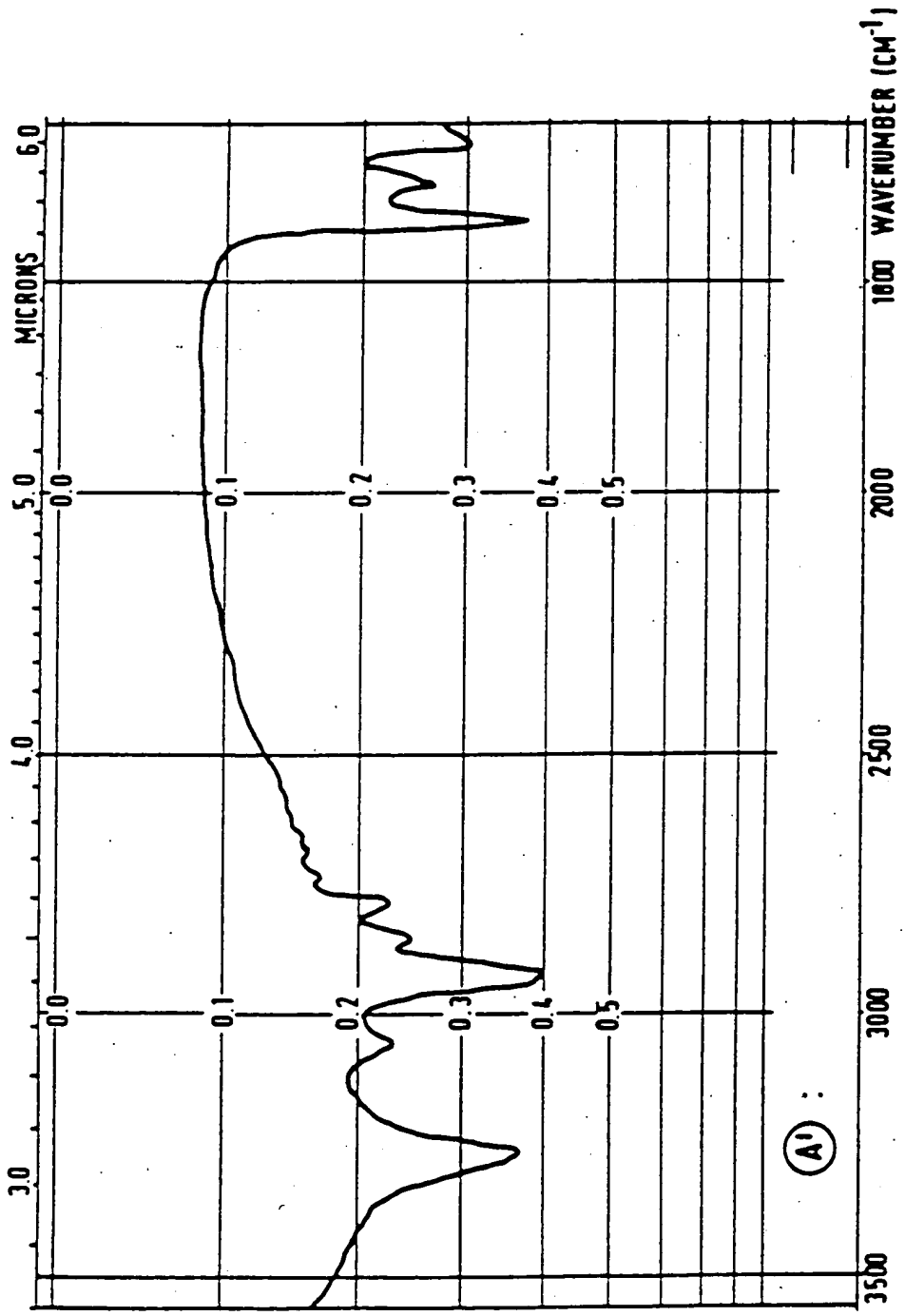

MICRONS
6.0
5.0
4.0
3.0
0.0
0.1
0.2
0.3
0.4
0.5
WAVENUMBER (CM-1)
1000
2000
2500
3000
3500
A'

FIG. 4 (PART 1)

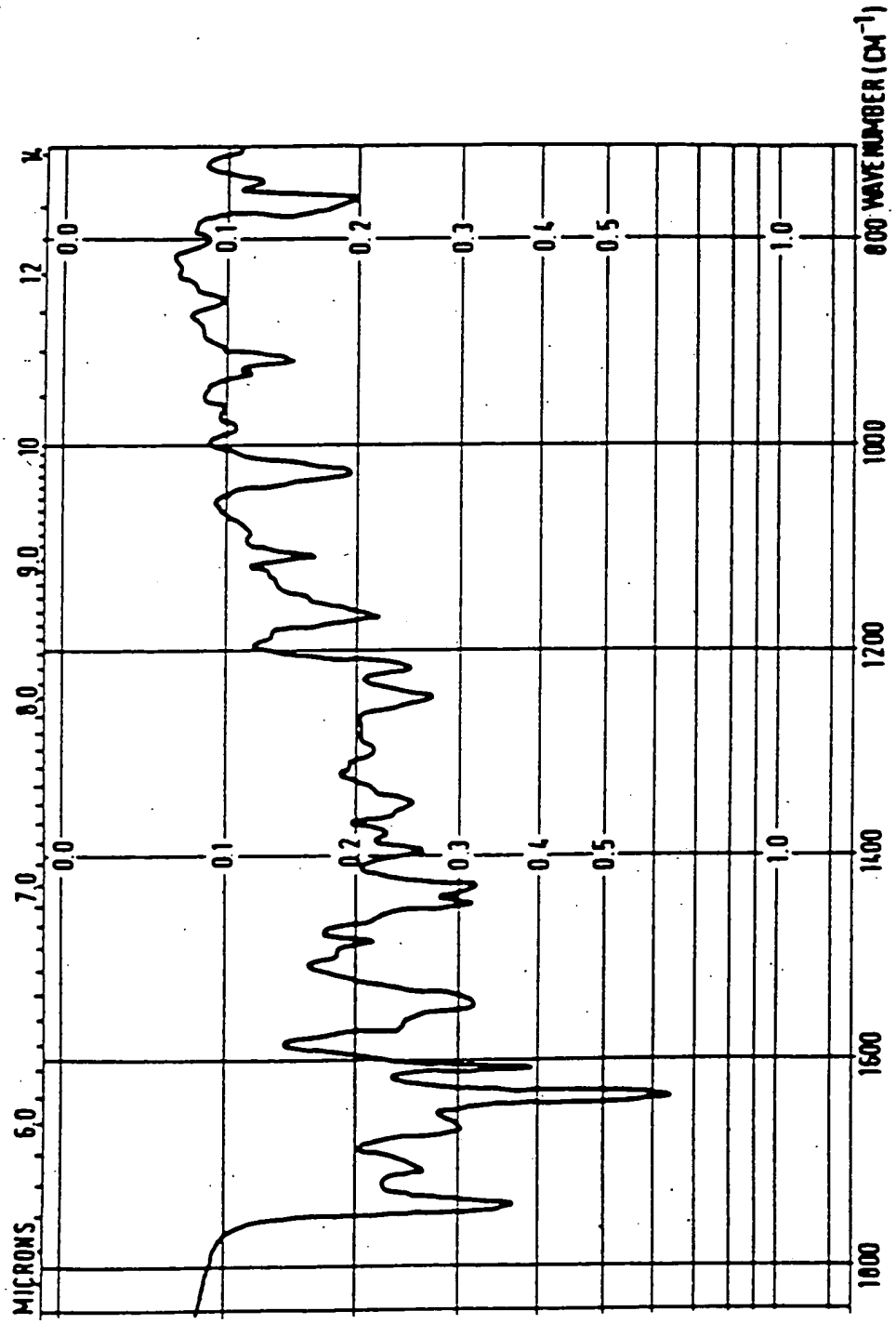

MICRONS
6.0
7.0
8.0
9.0
10
12
14
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1600
1400
1200
1000
800 WAVENUMBER (CM⁻¹)

FIG. 4 (PART 2)

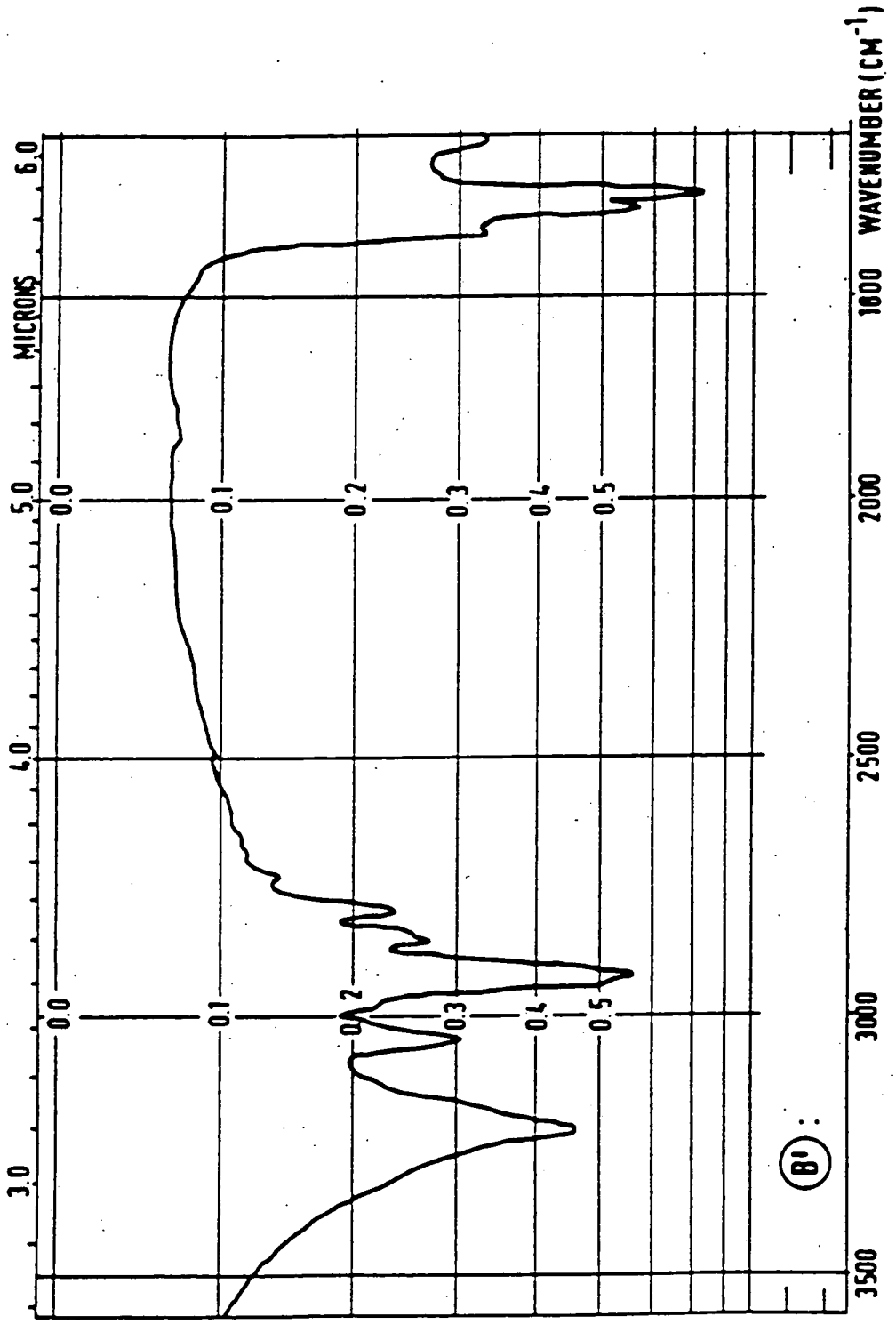

MICRONS
6.0
5.0
4.0
3.0
0.0
0.1
0.2
0.3
0.4
0.5
WAVENUMBER (CM⁻¹)
1600
2000
2500
3000
3500
B' :

FIG. 5 (PART 1)

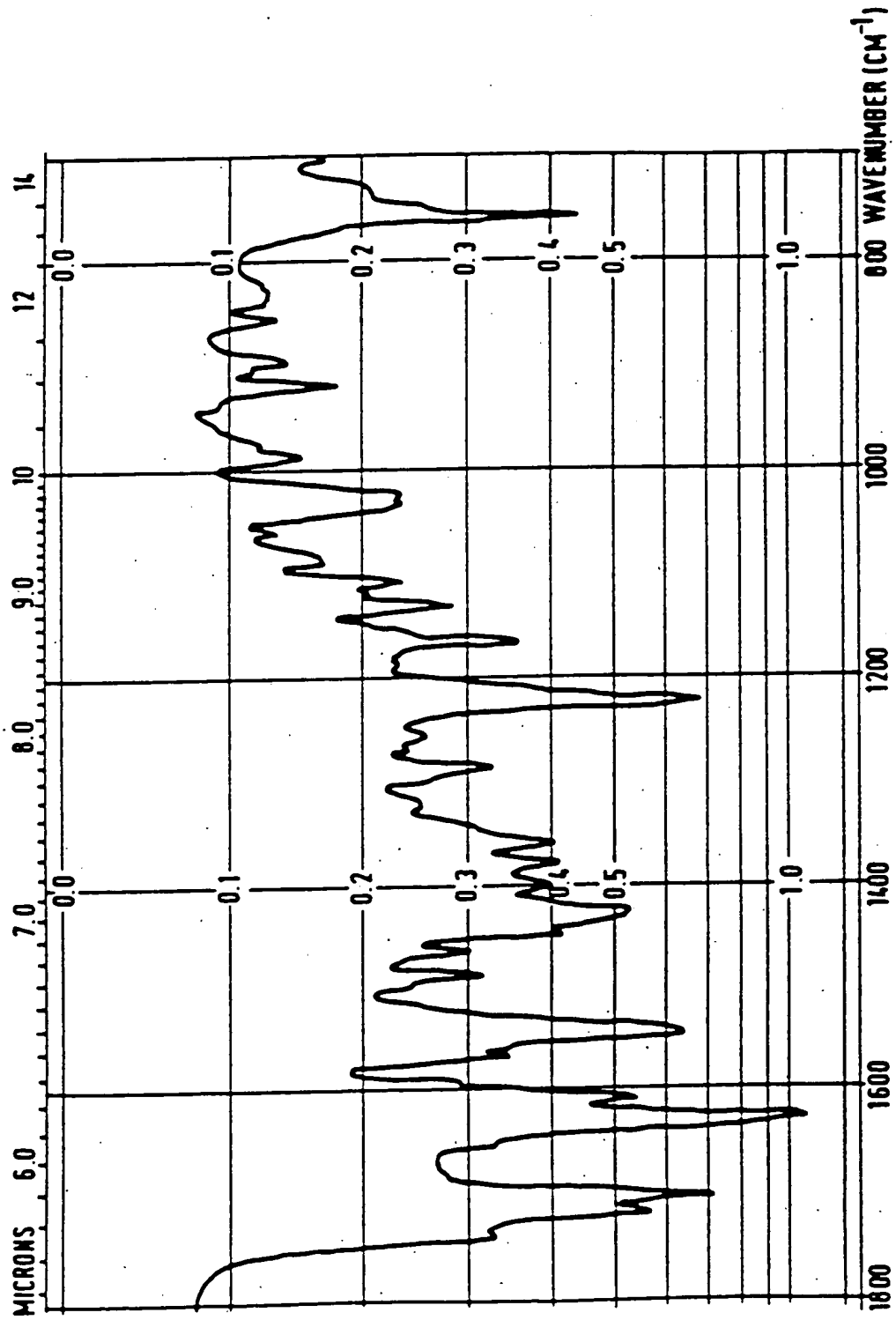

MICRONS
6.0
7.0
8.0
9.0
10
12
14
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1600
1400
1200
1000
800 WAVENUMBER (CM-1)
1800

FIG. 5 (PART 2)

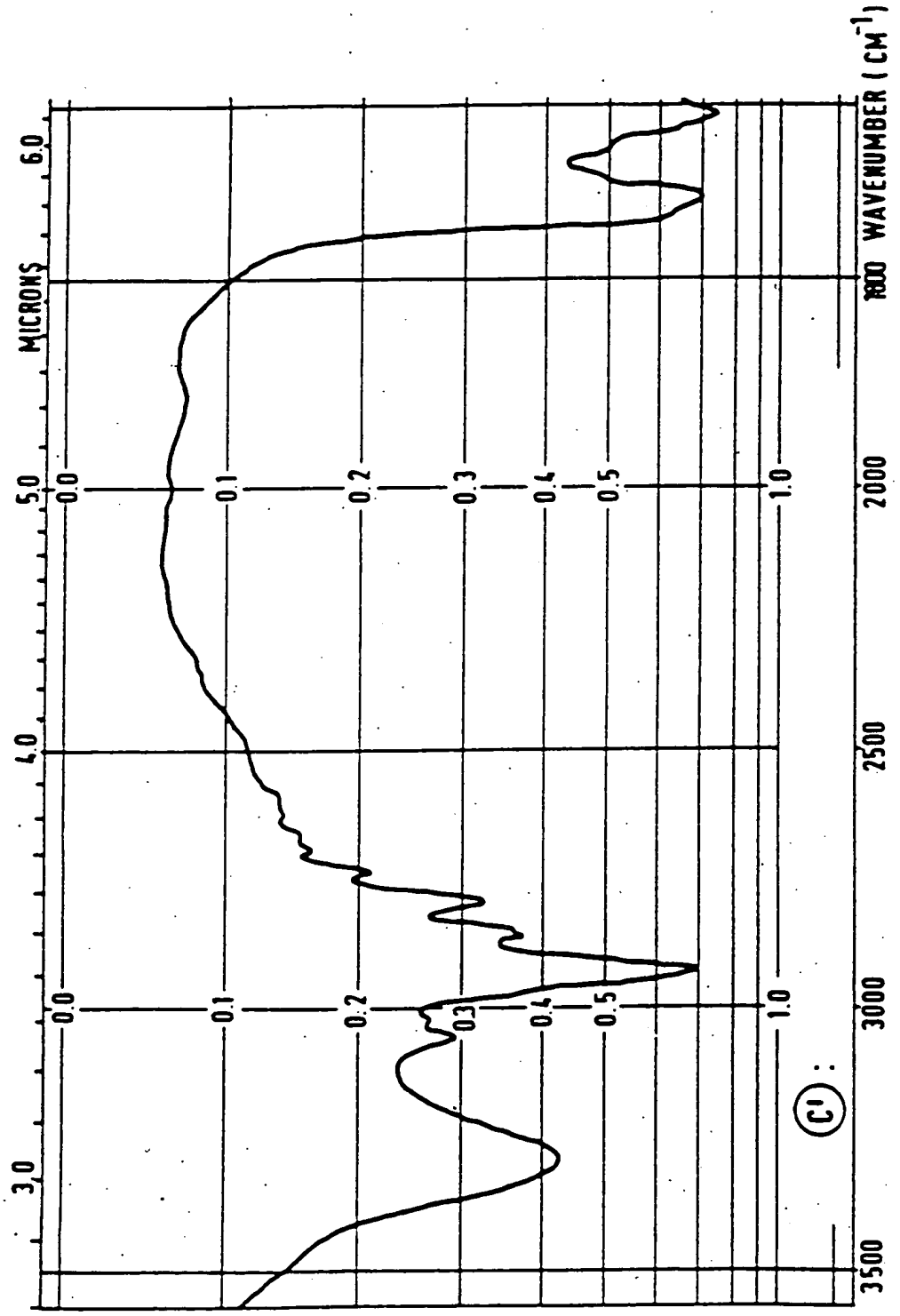

MICRONS
3.0
4.0
5.0
6.0
0.0
0.1
0.2
0.3
0.4
0.5
1.0
3500
3000
2500
2000
1800 WAVENUMBER (CM-1)
C':

FIG. 6 (PART 1)

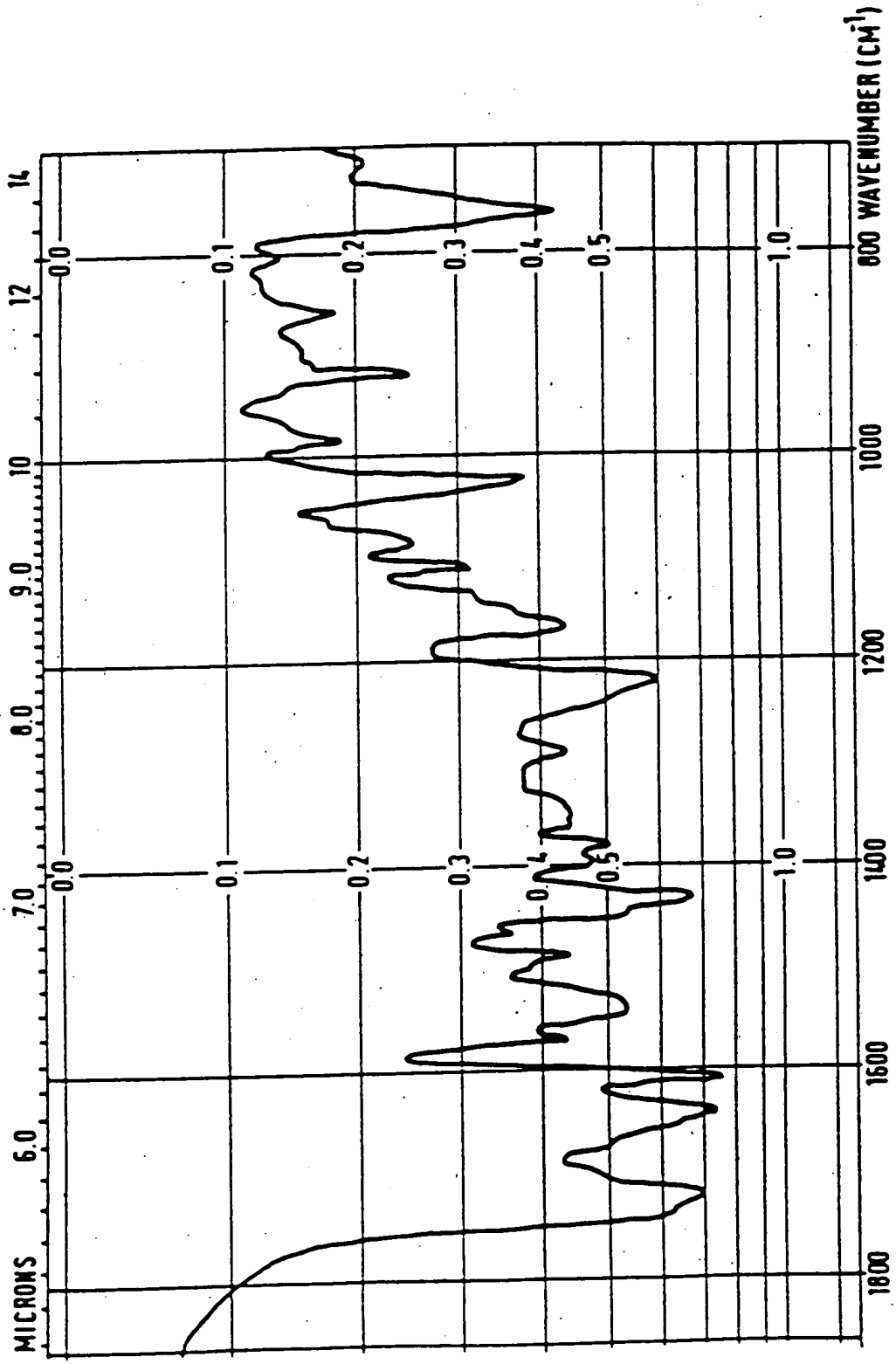

MICRONS
6.0
7.0
8.0
9.0
10
12
14
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1600
1400
1200
1000
800 WAVENUMBER (CM-1)
1800

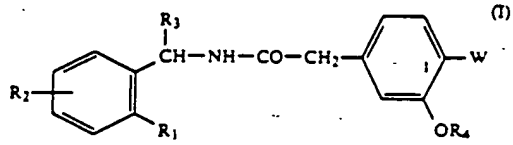
FIG. 6 (PART 2)

PHENYLACETIC ACID BENZYLAMIDES

This is a continuation of application Ser. No. 302,022, filed Jan. 25, 1989 (abandoned), and is a continuation-in-part of co-pending application Ser. No. 872,706 filed Jun. 10, 1986, (abandoned) which is a continuation-in-part of application Ser. No. 684,054 filed Dec. 10, 1984, now abandoned; and a continuation-in-part of co-pending application Ser. No. 878,921 filed Jun. 26, 1986 (abandoned).

This invention relates to novel phenylacetic acid benzylamides and their non-toxic salts, to methods of preparing these compounds, to pharmaceutical compositions containing them as active ingredients, and to a method of using them as hypoglycemics.

More particularly, the present invention relates to a novel class of compounds represented by the formula



(I)

wherein

R_1 represents an unbranched alkyleneimino group with 4 to 6 carbon atoms optionally mono- or di-(alkyl of 1 to 3 carbon atoms)-substituted;

R_2 represents a hydrogen or halogen atom or a methyl or methoxy group;

R_3 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group, an alkyl group with 1 to 2 carbon atoms substituted by a hydroxy, alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain from 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 to 3 carbon atoms and the cycloalkyl part can obtain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms;

R_4 represents a hydrogen atom, a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxyl, alkoxycarbonyl, cyanomethyl, 2-cyano-ethyl, 2-cyano-ethenyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonylethenyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group; and

when R_3 is other than hydrogen and/or the radical R_1 contains an optically active carbon atom, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position.

Specific embodiments of substituents R_1, R_2, R_3, R_4 and W are the following:

R_1: Pyrrolidino, piperidino, hexamethyleneimino, methyl-pyrrolidino, dimethyl-pyrrolidino, ethyl-pyrrolidino, 2-methyl-piperidino, 3-methyl-piperidino, 4-methyl-piperidino, 3,3-dimethyl-piperidino, cis-3,5-dimethyl-piperidino, trans-3,5-dimethyl-piperidino, ethyl-piperidino, diethyl-piperidino, methyl-ethyl-piperidino, propyl-piperidino, methyl-propyl-piperidino or isopropyl-piperidino.

R_2: Hydrogen, fluorine, chlorine, bromine, methyl or methoxy.

R_3: Hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, 2-methyl-n-butyl, 3-methyl-n-butyl, 2,2-dimethyl-propyl-n-hexyl, 4-methyl-n-pentyl, n-heptyl, phenyl, fluorophenyl, chlorophenyl, bromophenyl, methylphenyl, methoxyphenol, 1-propen-1-yl, 2-methyl-1-propen-1-yl, 3-methyl-3-buten-2-yl, 2-propen-1-yl, 2-methyl-2-propen-1-yl, 2-buten-1-yl, 2-methyl-2-buten-1-yl, 3-methyl-2-buten-1-yl, 2-buten-1-yl, 2-methyl-3-buten-1-yl, 3-methyl-3-buten-1-yl, 2-hexen-1-yl, 1-propyn-1-yl, 2-propyn-1-yl, 2-butyn-1-yl, 2-pentyn-1-yl, hydroxymethyl, 1-hydroxy-ethyl, 2-hydroxy-ethyl, methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, 1-methoxy-ethyl, 2-methoxy-ethyl, 1-ethoxy-ethyl, 2-ethoxy-ethyl, 2-n-propoxy-ethyl, 2-isopropoxy-ethyl, acetoxymethyl, propionyloxymethyl, 1-acetoxy-ethyl, 2-acetoxy-ethyl, 1-propionyloxy-ethyl, 2-propionyloxy ethyl, tetrahydrofuran-2-yl-methyl, 2-(tetrahydrofuran-2-yl)-ethyl, tetrahydrofuran-3-yl-methyl, tetrahydropyran-2-yl-methyl, 2-(tetrahydropyran-2-yl)-ethyl, tetrahydropyran-3-yl-methyl, cyclopropyl-methyl, cyclobutyl-methyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 2-cyclopropyl-ethyl, 2-cyclobutyl-ethyl, 2-cyclopenyl-ethyl, 2-cyclohexyl-ethyl, 2-cycloheptyl-ethyl, benzyl, 1-phenyl-ethyl, 2-phenyl-ethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl isopropoxycarbonyl, n-butoxycarbonyl, sec.butoxycarbonyl, isobutoxycarbonyl or tert.butoxycarbonyl.

R_4: Hydrogen, methyl, ethyl, n-propyl, isopropyl, allyl.

W: Methyl, hydroxymethyl, formyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec.butoxycarbonyl, isobutoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl, 3-phenylpropoxycarbonyl, cyanomethyl, 2-cyano-ethyl, 2-cyano-ethenyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, n-propoxycarbonylmethyl, n-butoxycarbonylmethyl, tert.butoxycarbonylmethyl, 2-methoxycarbonyl-ethyl, 2-ethoxycarbonyl-ethyl, 2-n-propoxycarbonyl-ethyl, 2-isopropoxycarbonyl-ethyl, 2-n-butoxycarbonyl-ethyl, 2-tert.butoxycarbonyl-ethyl, 2-methoxycarbonyl-ethenyl, 2-ethoxycarbonyl-ethenyl, 2-n-propoxycarbonyl-ethenyl or 2-tert.butoxycarbonylethenyl.

One subgeneric aspect is constituted by those compounds of the formula I wherein

R_1 represents a pyrrolidino, piperidino, 4-methyl-piperidino, 3-methyl-piperidino, 3,3-dimethyl-piperidino, 3,5-dimethyl-piperidino or hexamethyleneimino group;

R_2 represents a hydrogen, fluorine or chlorine atom;

R_3 represents a hydrogen atom, an alkyl group with 1 to 6 carbon atoms, a phenyl, methyl-phenyl, chloro-phenyl, methoxy-phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexyl-methyl, tetrahydrofuran-2-yl-methyl, tetrahydropyran-2-yl-methyl, propargyl, hydroxymethyl,

ethoxymethyl, acetoxymethyl, propionyloxymethyl, carboxy, methoxycarbonyl, ethoxycargonyl or propoxycarbonyl group or a branched or unbranched alkenyl group with 3 or 4 carbon atoms;

R_4 represents a methyl, ethyl or allyl group; and

W represents a methyl hydroxymethyl, formyl, carboxyl, benzyloxycarbonyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, cyanomethyl, 2-carboxy-ethyl, 2-ethoxycarbonyl-ethyl, 2-cyano-ethyl, 2-carboxy-ethenyl, 2-ethoxycarbonyl-ethenyl or 2-cyano-ethenyl group or an alkoxycarbonyl group with 1 to 4 carbon atoms in the alkoxy part; and

when R_3 is other than hydrogen and/or R_1 represents the 3-methyl-piperidino group, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position.

A preferred sugenus is constituted by those compounds of the formula I wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 1 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, tetrahydropyran-2-yl-methyl, cyclopropylmethyl or cyclohexylmethyl group;

R_4 represents a methyl ethyl or allyl group; and

W represents a carboxyl, methoxycarbonyl, ethoxycarbonyl or cyanomethyl group; and

the enantiomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

An especially preferred subgenus is constituted by those compounds of the formula I wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 3 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, cyclopropylmethyl or cyclohexylmethyl group;

R_4 represents a methyl or ethyl group; and

W represents a carboxyl group;

especially those compounds of the before mentioned preferred subgenus, wherein

R_3 represents an alkyl group with 3 to 6 carbon atoms, a 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group; and

the enantiomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

A preferred subgenus of the before mentioned compounds are those, wherein

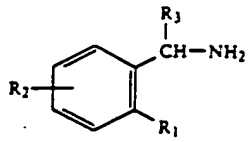
R_3 represents a n-propyl, n-butyl, isobutyl, sec.butyl, n-pentyl, 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group, especially when

R_3 represents a n-propyl, n-butyl, isobutyl, sec.butyl or n-pentyl group; and

the enantiomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

According to the invention, the new compounds are obtained by the following methods:

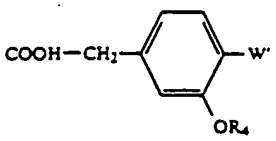
a) reacting an amine of formula



(II)

wherein

R_1 to R_3 are defined as hereinbefore, with a carboxylic acid of formula



(III)

wherein

R_4 is defined as hereinbefore and

W' has the meanings given for W hereinbefore, in which any carboxy group contained in the group W can be protected by a protecting group,

or with the reactive derivatives thereof optionally prepared in the reaction mixture, if necessary with subsequent splitting off of any protecting group used.

Examples of reactive derivatives of a compound of formula III which can be used include the esters thereof, such as the methyl, ethyl or benzyl esters, the thioesters such as the methylthio or ethylthioesters, the halides such as the acid chloride, the anhydride or imidazolides thereof.

The reaction is appropriately carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethyl formamide, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide. N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine, or pyridine, which can simultaneously be used as solvent, at temperatures of between −25° C. and 250° C., but preferably at temperatures of between −10° C. and the boiling temperature of the solvent used. The reaction can also be carried out without a solvent and furthermore any water formed during the reaction can be removed by azeotropic distillation, e.g. by heating with toluene using a water separator, or by adding a drying agent such as magnesium sulphate or a molecular sieve.

If necessary, the subsequent splitting off of a protecting group is preferably carried out by hydrolysis, conveniently either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as

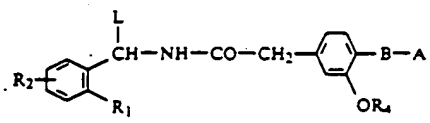
water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures of between −10° and 120° C., e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

A tert.butyl group used as protecting group can also be split off thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic acid, sulphuric, phosphoric or polyphosphoric acid.

Furthermore, a benzyl group used as protecting group can also be split off hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide.

b) In order to prepare compounds of formula I wherein R_3 represents a carboxy or alkoxycarbonyl group and W has the meanings given hereinbefore or W represents a carboxy, carboxymethyl, 2-carboxy-ethyl, 2-carboxy-ethenyl, alkoxycarbonyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group and R_3 has the meanings given hereinbefore:

Hydrolysis, thermolysis, hydrogenolysis or alcoholysis of a compound of formula



(IV)

wherein

R_1, R_2 and R_4 are as hereinbefore defined,

B represents a bond, a methylene, ethylene or ethenylene group,

A and L each represent a nitrile group or a group which can be converted into a carboxy group by hydrolysis, thermolysis or hydrogenolysis and

L additionally has the meanings given for R_3 hereinbefore.

Examples of hydrolysable groups include functional derivatives of the carboxy group and the unsubstituted or substituted amides, esters, thioesters, ortho esters, iminoethers, amidines or anhydrides thereof, the nitrile group, the tetrazolyl group, an optionally substituted 1,3-oxazol-2-yl or 1,3-oxazolin-2-yl group,

examples of thermolytically cleavable groups include esters with tertiary alcohols, e.g. the tert.butyl ester,

examples of hydrogenolytically cleavable groups include aralkyl groups, e.g. the benzyl group, and

examples of alcoholytically cleavable groups include the cyano group.

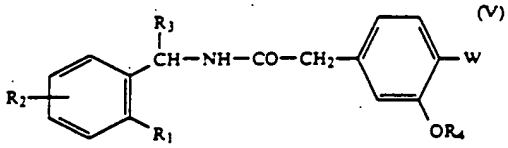
The hydolysis is conveniently carried out either in the presence of an acid such as hydrochloric sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between −10 and 120° C., e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture, and the alcoholysis of a cyano group is preferably effected in an excess of the corresponding alcohol such as methanol, ethanol or propanol and in the presence of an acid such as hydrochloric acid at elevated temperatures, e.g. at the boiling temperature of the reaction mixture.

If A and/or L in a compound of formula IV represents a nitrile or aminocarbonyl group, these groups can be converted into a corresponding carboxy compound by means of 100% phosphoric acid at temperatures of between 100 and 180° C., preferably at temperatures of between 120 and 160° C., or with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, the latter conveniently being used as solvent as well, at temperature of between 0 and 50° C.

If A and/or L in a compound of formula IV represents the tert butyloxycarbonyl group for example, the tert.butyl group can also be split off thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic, sulphuric, phosphoric or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures of between 40 and 100° C. If A and/or L in a compound of formula IV represents the benzyloxycarbonyl group for example, the benzyl group can also be split off hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, methanol/water, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide, preferably at temperatures of between 0 and 50° C., e.g. at ambient temperature and under a hydrogen pressure of from 1 to 5 bar. During hydrogenolysis, a compound containing halogen can simultaneously be dehalogenated, any double or triple bonds present can be hydrogenated and any benzyloxycarbonyl group present can be converted into a carboxy group.

c) In order to prepare compounds of formula I wherein R_4 represents a hydrogen atom:

Splitting off a protecting group from a compound of formula



(V)

wherein

R_1 to R_3 and W are as hereinbefore defined and

R_5 represents a protecting group for a hydroxy group.

Examples of protecting groups for R_5 include, for example, an alkyl, aralkyl or trialkylsilyl group, e.g. the methyl, ethyl, propyl, allyl, benzyl or trimethylsilyl group.

Depending on the protecting group used, the protecting groups mentioned above can be split off either by hydrolysis or by hydrogenolysis, optionally in a suitable solvent, at temperatures of between −78 and 250° C.

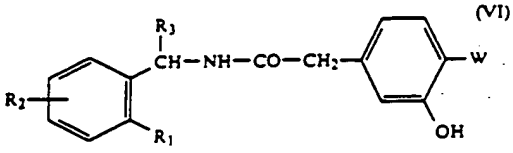
For example, ether splitting is carried out in the presence of an acid such as hydrochloric, hydrobromic or sulphuric acid, boron tribromide, aluminium trichloride or pyridine hydrochloride, conveniently in a suitable solvent such as methylene chloride, glacial acetic acid or water or in mixtures thereof at temperatures of between −78° and 250° C. The ether splitting is carried out in the presence of a proton acid conveniently at temperatures of between 0° and 150° C., preferably at

temperatures of between 50° and 150° C. or with a lewis acid preferably in a solvent such as methylene chloride at temperatures of between −78° and 20° C.

For example, any protecting group used such as a benzyl group can be split off hydrogenolytically with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide, preferably at ambient temperature, for example, and under a hydrogen pressure of from 1 to 5 bar.

d) In order to prepare compounds of formula I wherein R_4 represents methyl, ethyl or allyl group:

Reacting a compound of formula


(VI)

wherein

R_1 to R_3 and W are as hereinbefore defined, with a compound of formula


(VII)

wherein

R_6 represents methyl, ethyl or allyl group

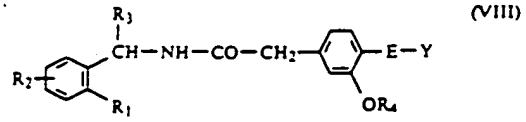
X represents a nucleophilically exchangeable group such as a halogen atom, a sulphonyloxy group or, together with the adjacent hydrogen atom, a diazo group, if R_6 represents an alkyl group with 1 to 3 carbon atoms, if necessary with subsequent hydrolysis.

The reaction is conveniently carried out with a corresponding halide, sulphonic acid ester, sulphuric acid diester or diazoalkane, e.g. with methyl iodide, dimethyl sulphate, ethyl bromide, diethyl sulphate, allyl bromide, ethyl p-toluenesulphonate, or diazomethane, optionally in the presence of a base such as sodium hydride, potassium carbonate, sodium hydroxide, potassium tert.butoxide or triethylamine in a suitable solvent such as acetone, diethylether, tetrahydrofuran, dioxan or dimethylformamide at temperatures of between 0° and 100° C., preferably at temperatures of between 20° and 50° C. If in a compound of formula VI R_3 represents a carboxy group and/or W represents a carboxy, carboxymethyl, 2-carboxy-ethyl or 2-carboxy-ethenyl group, this compound can simultaneously be converted into the corresponding ester compound. A compound thus obtained is, if necessary by cleaving the ester group, converted into the desired compound of formula I.

The cleaving of the ester group is carried out hydrolytically, conveniently either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures of between −10° and 120° C., e.g. at temperatures of between ambient temperature and the boiling point of the reaction mixture.

e) In order to prepare compounds of formula I wherein W represents a cyanomethyl or 2-cyano-ethyl group:

Reacting a compound of formula


(VIII)

wherein

R_1 to R_4 are as hereinbefore defined,

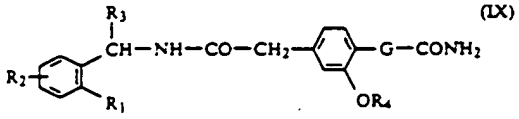
E represents a methylene or ethylene group and

Y represents a nucleophilically exchangeable group such as a halogen atom or a sulphonyloxy group, e.g. a chlorine, bromine or iodine atom or a methane-sulphonyloxy or p-toluenesulphonyloxy group, with an alkali metal cyanide such as sodium or potassium cyanide.

The reaction is conveniently carried out in a suitable solvent such as dimethylsulphoxide or dimethylformamide at temperatures of between 0° and 100° C., preferably at temperatures of between 20° and 50° C., or in a two-phase system such as methylene chloride/water in the presence of a phase transfer catalyst such as benzyl-tributyl-ammonium chloride at temperatures of between 10° and 100° C., preferably at temperatures of between 20° and 50° C.

f) In order to prepare compounds of formula I wherein W represents a cyanomethyl, 2-cyano-ethyl or 2-cyano-ethenyl group:

Dehydration of a compound of formula


(IX)

wherein

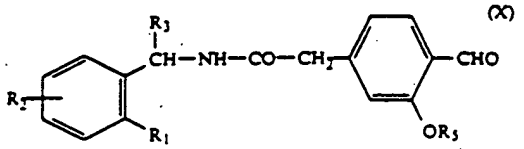
R_1 to R_4 are as hereinbefore defined and

G represents a methylene, ethylene or ethenylene group.

The dehydration is carried out with a water-cleaving agent such as phosphorus pentoxide, phosphorus oxychloride, triphenylphosphine/carbon tetrachloride or p-toluenesulphonic acid chloride, optionally in a solvent such as methylene chloride, acetonitrile or pyridine at temperatures of between 0° and 100° C., preferably at temperatures of between 20° C. and 180° C.

g) In order to prepare compounds of formula I wherein W represents a 2-cyano-ethenyl, 2-carboxy-ethenyl or 2-alkoxycarbonyl-ethenyl group:

Reacting a compound of formula


(X)

wherein

R_1 to R_4 are as hereinbefore defined, with a corresponding acetic acid derivative of formula


(XI)

wherein Q represents a carboxy, alkoxycarbonyl or cyano group and

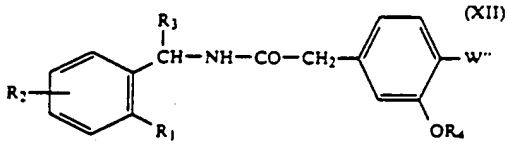
Z represents a hydrogen atom, an alkoxycarbonyl, dialkylphosphono or triphenylphosphonium halide group, optionally with subsequent hydrolysis and-/or decarboxylation.

The reaction is conveniently carried out in a solvent such as diethylether, tetrahydrofuran, 1,2-dimethoxyethane, dioxan, dimethylformamide, toluene or pyridine in the presence of a base as condensation agent such as sodium carbonate, sodium hydride, potassium tert-butoxide or piperidine at temperatures of between 0° and 100° C., preferably at temperatures of between 20° and 80° C.

The subsequent hydrolysis and/or decarboxylation is conveniently carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water-/ethanol, water/isopropanol or water/dioxan at temperatures of between −10° C. and 120° C., e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

h) In order to prepare compounds of formula I wherein W represents a 2-carboxy-ethyl, 2-alkoxycarbonyl-ethyl or 2-cyano-ethyl group:

Reduction of a compound of formula



(XII)

wherein

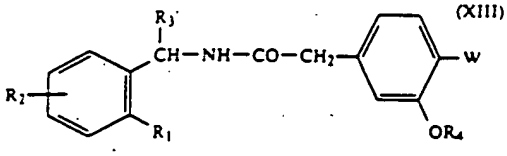
R_1 to R_4 are as hereinbefore defined and

W'' represents a 2-carboxy-ethenyl, 2-alkoxycarbonyl-ethenyl or 2-cyano-ethenyl group.

The reduction is preferably carried out in a suitable solvent such as methanol, ethanol, isopropanol, ethyl acetate, dioxan, tetrahydrofuran, dimethylformamide, benzene or benzene/ethanol with hydrogen in the presence of a suitable hydrogenation catalyst such as palladium/charcoal, Raney nickel or tris-#[triphenylphosphine#*-rhodium(I)chloride at temperatures of between 0° and 100° C., under a hydrogen pressure of from 1 to 5 bar or, if W'' contains a cyano group, with nascent hydrogen, e.g. with magnesium/methanol, or with a copper hydride complex, e.g. with the complex prepared from copper bromide, sodium bis(2-methoxyethoxy)-aluminium hydride and sec.butanol, at temperatures of between −78° and 50° C. Other groups can be reduced at the same time, e.g. a benzyloxy group can be reduced to the hydroxy group, an alkenyl or alkynyl group can be reduced to the corresponding alkyl group or a formyl group can be reduced to the hydroxymethyl group, or they can be replaced by hydrogen atoms, e.g. a halogen atom can be replaced by a hydrogen atom.

i) In order to prepare compounds of formula I wherein R_3 represents an alkyl group with 1 or 2 carbon atoms substituted by an alkoxy or alkanoyloxy group:

Reacting a compound of formula



(XIII)

wherein

R_1, R_2, R_4 and W are as hereinbefore defined and R_3' represents an alkyl group with 1 or 2 carbon atoms substituted by a hydroxy group, with a compound of formula

$$U-R_7 \qquad \text{(XIV)}$$

wherein

R_7 represents an alkyl group with 1 to 3 carbon atoms or an acetyl or propionyl group and

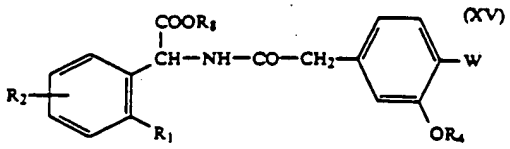
U represents a nucleophilically exchangeable group such as a halogen atom, a sulphonyloxy group, an acetoxy or propionyloxy group or, together with the adjacent hydrogen atom, represents a diazo group if R_7 represents an alkyl group with 1 to 3 carbon atoms, optionally with subsequent hydrolysis.

The reaction is conveniently carried out with a corresponding halide, anhydride, sulphonic acid ester, sulphuric acid diester or diazoalkane, e.g. with methyl iodide, dimethyl sulphate, ethyl iodide, diethyl sulphate, n-propyl iodide, isopropyl bromide, acetyl chloride, acetic hydride, propionic acid chloride propionic acid anhydride, ethyl p-toluenesulphonate or isopropylmethanesulphonate, optionally in the presence of a base such as sodium hydride, potassium carbonate, sodium hydroxide, potassium tert.butoxide or triethylamine, or with diazomethane, optionally in the presence of a Lewis acid, e.g. boron trifluoride, preferably in a suitable solvent such as acetone, diethylether, tetrahydrofuran, dioxan, pyridine or dimethylformamide at temperatures of between 0° and 100° C., preferably at temperatures of between 20° and 50° C., in which an anhydride used as the acylating agent can simultaneously also be used as solvent.

If in a compound of formula XIII W represents a carboxy, carboxymethyl, 2-carboxy-ethyl or 2-carboxyethenyl group and/or R_4 represents a hydrogen atom, this can simultaneously be converted into the corresponding ester and/or ether compound.

k) In order to prepare compounds of formula I wherein R_3 represents an alkoxycarbonyl group:

Reacting a compound of formula



(XV)

wherein

R_1, R_2, R_4 and W are as hereinbefore defined and

R_8 represents a hydrogen atom or alkali metal atom, or the reactive derivatives thereof optionally prepared in the reaction mixture, with a compound of formula

$$T-R_9 \qquad \text{(XVI)}$$

wherein

R_9 represents an alkyl group with 1 to 4 carbon atoms and

T represents a hydroxy group or a nucleophilically exchangeable group such as a halogen atom or a sulphonyloxy group, or together with the adjacent hydrogen atom of the group R_9 represents a diazo group, optionally followed by hydrogenolysis if W contains a benzyloxycarbonyl group.

An example of a reactive derivative of a compound of formula XV is the imidazolide thereof.

The reaction is conveniently carried out in the corresponding alcohol as solvent or in a suitable solvent such as methylene chloride, chloroform, ether, tetrahydrofuran, dioxan, dimethylformamide, benzene or toluene, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of hydrogen chloride, sulphuric acid, ethyl chloroformate, thionyl-chloride, carbon tetrachloride/triphenylphosphine, carbonyldiimidazole or N,N'-dicyclohexylcarbodiimide or the isourea ethers thereof, optionally in the presence of a reaction accelerator such as copper chloride and optionally in the presence of an inorganic base such as potassium carbonate or a tertiary organic base such as triethylamine, 1,8-diazabicyclo[5,4,0]-undec-7-ene or pyridine, or by transesterification, e.g. with a corresponding carbonic acid diester, at temperatures of between −20° C. and 100° C., but preferably at temperatures of between −10° C. and the boiling temperature of the solvent used.

The optional subsequent hydrogenolysis is carried out in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide.

If W in a compound of formula XV contains a carboxy group, this can be converted during the reaction into the corresponding alkoxycarbonyl group.

l) In order to prepare compounds of formula I wherein

R_4 represents a hydrogen atom, methyl, ethyl or allyl group and

W represents a methyl, formyl, carboxy, carboxymethyl, 2-carboxy-ethyl, alkoxycarbonyl, alkoxycarbonylmethyl or 2-alkoxycarbonylethyl group, in which the alkoxy part can contain from 1 to 4 carbon atoms.

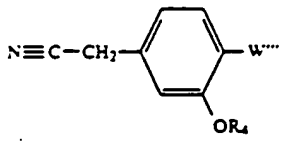
Reacting a compound of formula

(XVII)

wherein

R_1 and R_2 are as hereinbefore defined and

R_3'' represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or by a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by an alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, wherein the alkoxy part can contain 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 or 3 carbon atoms and the cycloalkyl part can contain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms, with a compound of formula



(XVIII)

wherein

R_4 is as hereinbefore defined and

W'''' represents a methyl, formyl, carboxy, carboxymethyl, 2-carboxy-ethyl, alkoxycarbonyl, alkoxycarbonylmethyl or 2-alkoxy-carbonyl-ethyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms.

The reaction is carried out in the presence of a strong acid which can simultaneously serve as solvent, preferably in concentrated sulfuric acid, at temperatures of between 0° and 150° C., preferably at temperatures of between 20° and 100° C.

If in a compound of formula XVIII R_4 represents an allyl group, this is split off during the reaction or after the reaction by the addition of water.

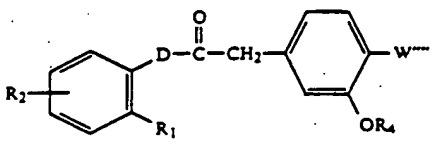
m) In order to prepare compounds of formula I wherein

R_4 represents a hydrogen atom, a methyl or ethyl group,

R_3 represents an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by an alkoxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group in which the alkoxy part can contain 1 to 3 carbon atoms and the cycloalkyl part can contain 5 to 7 carbon atoms, and

W represents a methyl, hydroxymethyl, carboxy, cyanomethyl, 2-cyano-ethyl, carboxymethyl, 2-carboxy-ethyl, alkoxycarbonyl, alkoxycarbonylmethyl or 2-alkoxycarbonyl-ethyl group in which the alkoxy part can contain from 1 to 4 carbon atoms.

Reduction of a compound of formula

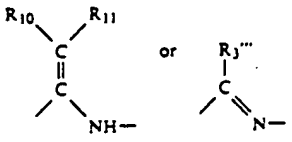


(XIX)

wherein

R_1, R_2 and R_4 are as hereinbefore defined and

D represents a group of formula



in which R_3''' represents a phenyl group optionally substituted by a halogen atom or by a methyl or methoxy group.

R_{10} and R_{11} together with the carbon atom between them represent an alkylidene group with 1 to 7 carbon atoms, an alkylidene group with 1 or 2 carbon atoms substituted by an alkoxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain 1 to 3 carbon atoms and the cycloalkyl part can contain 5 to 7 carbon atoms, and

W'''' represents a methyl, hydroxymethyl, formyl, carboxy, cyanomethyl, 2-cyano-ethyl, 2-cyano-ethyl, carboxymethyl, 2-carboxy-ethyl, 2-carboxy-ethenyl, alkoxycarbonyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonylethenyl group, in which the alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group.

The reduction is preferably carried out with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal or Raney-nickel in a suitable solvent such as methanol, ethanol, isopropanol, ethyl acetate, dioxan, tetrahydrofuran, dimethylformamide, benzene or benzene/ethanol at temperatures of between 0° and 100° C., preferably at temperatures of between 20° and 50° C., and under a hydrogen pressure of from 1 to 5 bar. When a suitable chiral hydrogenation catalyst is used, such as a metal ligand complex e.g. [(2S), (4S)-1-tert.butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine-rhodium-cyclooctadiene(1,5)]-perchlorate, the addition of hydrogen occurs enantioselectively. Moreover, in the catalytic hydrogenation, other groups can also be reduced, e.g. a benzyloxy group can be reduced to the hydroxy group or a formyl group can be reduced to the hydroxy methyl group, or they can be replaced by hydrogen atoms, e.g. a halogen atom can be replaced by a hydrogen atom.

If a compound of the formula I is obtained wherein R_2 is halogen and/or R_3 is halophenyl and/or W is hydroxymethyl which has been converted into halomethyl, it may, if desired, be converted by d-halogenation into a corresponding compound of the formula I wherein R_2 is hydrogen and/or R_3 is phenyl and/or W is methyl.

If a compound of the formula I is obtained wherein W is carboxyl, this compound may, if desired, be converted by esterification into a corresponding compound of the formula I wherein W is alkoxycarbonyl or phenylalkoxycarbonyl.

If a compound of the formula I is obtained wherein W is carboxyl, alkoxycarbonyl or phenylalkoxycarbonyl, this compound may be converted by reduction into a corresponding compound of the formula I wherein W is formyl or hydroxymethyl.

If a compound of the formula I is obtained wherein W is hydroxymethyl, this compound may be converted by oxidation into a corresponding compound of the formula I wherein W is formyl or carboxyl.

If a compound of the formula I is obtained wherein W is carboxyl, this compound may be converted, via a sulfonic acid hydrazide and subsequent disproportionation, into a corresponding compound of the formula I wherein W is formyl.

The subsequent dehalogenation is advantageously carried out by catalytic hydrogenation, for example with palladium-on-charcoal, in a suitable solvent such as methanol, ethanol, tetrahydrofuran, dioxane, dimethylformamide or ethyl acetate, optionally in the presence of a base such as triethylamine, and at temperatures between 20° and 100° C., preferably at 20° to 50° C.

The subsequent esterification is advantageously carried out in a suitable solvent, for instance in a corresponding alcohol, pyridine, toluene, methylene chloride, tetrahydrofuran or dioxane, in the presence of an acid-activating and/or dehydrating agent such as thionyl chloride, ethyl chloroformate, carbonyldiimidazole or N,N'-dicyclohexylcarbodiimide or the isourea ethers thereof, optionally in the presence of a reaction accelerator such as copper chloride, or by trans-esterification, for instance with a corresponding carbonic acid diester, at temperatures between 0° and 100° C., but preferably at temperatures between 20° and the boiling point of the solvent which is used.

The subsequent reduction is preferably carried out with a metal hydride, for example with a complex metal hydride such as lithium aluminum hydride, lithium borohydride or lithium borohydride/trimethylborate, in a suitable solvent such as diethyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane at temperatures between 0° and 100° C., but preferably at temperatures between 20° C. and 60° C.

The subsequent oxidation of an alcohol is preferably carried out with an oxidizing agent, for instance with pyridinium chlorochromate or manganese dioxide, in a suitable solvent such an chloroform or methylene chloride at temperatures between as chloroform or methylene chloride at temperatures between −10° and 50° C., but preferably at temperatures between 0° and 20° C.

The subsequent disproportionation of a sulfonic acid hydrazide, obtained by reacting a corresponding hydrazine with a suitable reactive carboxylic acid derivative, is carried out in the presence of a base such as sodium carbonate in a solvent such as ethylene glycol at temperatures between 100° C. and 200° C., but preferably at 160°–170° C.

If according to the invention a racemic compound of formula I is obtained wherein R_3 has the meanings given hereinbefore with the exception of the hydrogen atom, this compound can be resolved into the enantiomers thereof via the diastereomeric adducts, complexes, salts or derivatives thereof.

The subsequent racemate splitting is preferably carried out by column or HPL chromatography by forming diastereomeric adducts or complexes in a chiral phase.

The compounds of formula I obtained according to the invention can also be converted into the salts thereof and, for pharmaceutical use, into the nontoxic, pharmaceutically acceptable salts thereof with inorganic or organic acids or bases. Suitable acids include, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, lactic, citric, tartaric, succinic, maleic, fumaric, aspartic or glutamic acid and suitable bases include sodium hydroxide, potassium hydroxide, calcium hydroxide, cyclohexylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine or arginine.

The compounds of formulae II to XIX used as starting materials are known from the literature in some cases or can be obtained by methods known per se.

Thus, for example, a compound of formula II is obtained by reducing a corresponding nitrile with lithium aluminium hydride or with catalytically activated hydrogen, by reacting a corresponding nitrile with a corresponding grignard or lithium compound and subsequent lithium-aluminium hydride reduction or subse-

quent hydrolysis to form the ketimine which is subsequently reduced with catalytically activated hydrogen, with a complex metal hydride or with nascent hydrogen, by hydrolysis or by hydrazinolysis of a corresponding phthalimido compound, by reacting a corresponding ketone with ammonium formate and subsequent hydrolysis or with an ammonium salt in the presence of sodium cyanoborohydride, by reduction of a corresponding oxime with lithium aluminium hydride, with catalytically activated or nascent hydrogen, by reduction of a corresponding N-benzyl or N-1-phenylethyl Schiff's base e.g. with a complex metal hydride in either or tetrahydrofuran at temperatures of between −78° C. and the boiling temperature of the solvent used with subsequent splitting off of the benzyl or 1-phenylethyl group by catalytic hydrogenation, by lithiation of a corresponding benzylideneimino-benzyl compound, e.g. by means of lithium-diisopropylamide at temperatures of between −78° and 20° C., subsequent reaction with a corresponding halogen compound, e.g. with a corresponding bromoalkyl, bromoalkenyl or bromoalkinyl compound, and subsequent hydrolysis, by Ritter reaction of a corresponding alcohol with potassium cyanide in sulfuric acid, by Hofmann, Curtius, Lossen or Schmidt degradation of a corresponding compound or by converting a corresponding benzaldehyde into a corresponding glycine derivative, e.g. using sodium cyanide/ammonium carbonate in ethanol/water into a corresponding hydantoin derivative, hydrolysis thereof, and, if necessary, subsequent esterification and, if necessary, subsequent reduction, e.g. with a complex metal hydride in ether or tetrahydrofuran.

An amine of formula II thus obtained having a chiral centre can be resolved into its enantiomers by racemate splitting, e.g. by fractional crystallization of the diastereomeric salts with optically active acids and subsequent decomposition of the salts or by column of HPL chromatograpy, optionally in the form of the acyl derivative thereof, or by forming diasteromeric compounds, separating them and subsequently splitting them.

Moreover, an optically active amine of formula II can also be prepared by enantioselective reduction of a corresponding ketimine using complex boron or aluminium hydrides in which some of the hydride hydrogen atoms have been replaced by optically active alkoxide groups, or by means of hydrogen in the presence of a suitable chiral hydrogenation catalyst or analogously starting from a corresponding N-benzyl or N-(1-phenethyl)-ketimine or from a corresponding N-acyl-ketimine or enimide and optionally subsequently splitting off the benzyl, 1-phenethyl or acyl group.

Furthermore, an optically active amine of formula II can also be prepared by diastereoselective reduction of a corresponding ketimine or hydrazone substituted at the nitrogen atom with a chiral group, using a complex or non-complex boron or aluminium hydride in which some of the hydride hydrogens can optionally be replaced by corresponding alkoxide, phenoxide or alkyl groups or using hydrogen in the presence of a suitable hydrogenation catalyst optionally with subsequent splitting off of the chiral auxiliary group by catalytic hydrogenolysis or hydrolysis.

Moreover, an optically active amine of formula II can also be prepared by diastereo-selective addition of a corresponding organometallic compound, preferably a grignard or lithium compound, to a corresponding aldimine substituted with a chiral group at the nitrogen atom, by subsequent hydrolysis and optionally subsequent splitting off of the chiral auxiliary group by catalytic hydrogenolysis or hydrolysis.

The compounds of formulae IV, V, VI, VIII, IX, X, XII, XIII and XV used as starting materials are obtained by reacting a corresponding amine with a suitable carboxylic acid or a reactive derivative thereof and, if necessary, subsequently splitting off any protecting group used.

A compound of formula XVII used as starting material is obtained by reducing a corresponding carbonyl compound by reacting a corresponding carbonyl compound with a corresponding grignard or lithium reagent or by hydrolysis or alcoholysis of a corresponding cyanohydrin and, if necessary, subsequent esterification.

A compound of formula XIX used as starting material is obtained by acylating a corresponding ketimine or the organometallic complex thereof with a corresponding carboxylic acid or reactive derivatives thereof, optionally with tautomerization.

The following examples illustrate the present invention and will enable others skilled in the art to understand it more completely. It should be understood, however, that the invention is not limited solely to the particular examples given below.

EXAMPLE 1

Ethyl
2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl-}aminocarbonylmethyl]-benzoate

2 g (7.9 mmols) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid, 2.46 g (9.38 mmols) of triphenylphosphine, 1.7 ml (12.3 mmols) of triethylamine and 0.76 ml (7.9 mmols) of carbon tetrachloride were added to a solution of 1.84 g (7.9 mmols) of 1-(2-piperidinophenyl)-1-butylamine in 19 ml of acetonitrile, and the mixture was stirred for two days at room temperature. It was then evaporated in vacuo, and the residue was taken up in a mixture of ethyl acetate and water. The organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 5/1).

Yield: 3 g (81% of theory).

M.p. 113°–115° C. (petroleum ether).

Calculated: C—72.07%; H—8.21%; N—6.00%.
Found: C—72.18%; H—8.27%; N—6.16%.

The following compounds were prepared by a procedure analogous to that described in Example 1:

(a) Methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-ethylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 78% of theory.

M.p. 82°–85° C.

Calculated: C—70.22%; H—7.37%; N—6.82%.
Found: C—70.54%; H—7.49%; N—6.75%.

(b) Ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl}-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 77% of theory.

M.p. 149°–151° C.

Calculated: C—7.437%; H—7.25%; N—5.60%.
Found: C—74.69%; H—6.44%; N—5.59%.

(c) Methyl 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 65% of theory.

M.p. 189°-190° C.

Calculated: C—73.70%; H—6.83%; N—5.93%. Found: C—73.51%; H—6.75%; N—5.86%.

(d) Ethyl 2-ethoxy-4-[N-1-{2-piperidino-phenyl}-1-ethyl)aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-ethylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 69% of theory.

M.p. 92°-93° C.

Calculated: C—71.21%; H—7.81%; N—6.39%. Found: C—71.29%; H—8.03%; N—6.58%.

(e) Ethyl 2-ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(5-chloro-2-piperidino-phenyl)-1-propylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 80% of theory.

M.p. 110°-112° C.

Calculated: C—66.58%; H—7.24%; N—5.75%; Cl—7.28. Found: C—66.61%; H—7.34%; N—5.86%; Cl—7.35%.

(F) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-pentylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 63% of theory.

M.p. 113°-115° C.

Calculated: C—72.47%; H—8.39%; N—5.83%. Found: C—72.66%; H—8.26%; N—5.99%.

(g) Ethyl 2-ethoxy-4-[N-{1-(2-pyrrolidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-pyrrolidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 50% of theory.

M.p. 85°-87° C.

Calculated: C—71.65%; H—8.02%; N—6.19%. Found: C—71.90%; H—8.37%; N—6.34%.

(h) Ethyl 2-ethoxy-4-[N-{1-(2-(4-methyl-piperidino)-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-[2-(4-methyl-piperidino)-phenyl]-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 44% of theory.

M.p. 127°-128° C.

Calculated: C—72.47%; H—8.39%; N—5.83%. Found: C—72.20%; H—8.23%; N—5.69%.

(i) Ethyl 2-ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-hexamethyleneimino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 44% of theory.

M.p. 97°-100° C.

Calculated: C—72.47%; H—8.39%; N—5.83%. Found: C—72.41%; H—8.50%; N—5.66%.

(k) Ethyl 2-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(4-methyl-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 68% of theory.

M.p. 113°-114° C.

Calculated C—72.47%; H—8.39%; N—5.83%. Found: C—72.36%; H—8.31%; N—5.91%.

(l) Ethyl 2-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(6-methyl-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 62% of theory.

M.p. <20° C.

Calculated: C—72.47%; H—8.39%; N—5.83%. Found: C—72.30%; H—8.50%; N—5.72%.

(m) Ethyl 2-ethoxy-4-[N-{1-(6-chloro-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(6-chloro-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 85% of theory.

M.p. <20° C.

Calculated: C—67.12%; H—7.44%; N—5.50%; Cl—7.08%. Found: C—67.60%; H—7.77%; N—5.92%; Cl—7.24%.

(n) Ethyl 2-ethoxy-4-[N-{1-(4-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(4-methoxy-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 65% of theory.

M.p. 109°-110° C.

Calculated: Mol peak m/e=496 Found: Mol. peak m/e=496.

(o) Ethyl 2-ethoxy-4-[N-{1-(5-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(5-methoxy-2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 31% of theory.

M.p. 117°-120° C.

Calculated: Mol. peak m/e=496 Found: Mol. peak m/e=496.

(p) Ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 4-ethoxycarbonyl-3-hydroxy-phenylacetic acid.

Yield: 46% of theory.

M.p. 133°-134° C.

Calculated: C—71.21%; H—7.81%; N—6.39%. Found: C—71.08%; H—7.91%; N—6.45%.

(q) Methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 67% of theory.

M.p. 128°-131° C.

Calculated: C—71.21%; H—7.81%; N—6.39%. Found: C—71.46%; H—7.80%; N—6.06%.

(r) n-Propyl 2-n-propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-n-propoxy-4-n-propoxycarbonyl-phenylacetic acid.

Yield: 56% of theory.

M.p. 88°-89° C.

Calculated: C—72.84%; H—8.56%; N—5.55%. Found: C—72.80%; H—8.78%; N—5.78%.

(s) Ethyl 2-ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)aminocarbonylmethyl]-benzoate

Prepared from 5-chloro-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 65% of theory.

M.p. 106°-108° C.

Calculated: C—65.41%; H—6.81%; N—6.10%; Cl-7.73%. Found: C—65.81%; H—6.89%; N—6.11%; Cl—7.62%.

(t) Ethyl (−)-2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoate

Prepared from (−)-α-phenyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 87% of theory.

M.p. 110°-111° C.

Calculated: mol peak m/e=500 Found: mol peak m/e=500.

Specific rotation: $[\alpha]_D^{20} = -6.3°$ (c=1, methanol).

(u) Ethyl 2-ethoxy-4-[N-(6-methyl-α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared from 6-methyl-α-phenyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 39% of theory.

M.p. <20° C.

Calculated: C—74.68%; H—7.44%; N—5.44%. Found: C—74.81%; H—7.56%; N—5.32%.

(v) Ethyl 2-ethoxy-4-[N-{α-(4-methyl-phenyl)-2-piperidinobenzyl}-aminocarbonylmethyl]-benzoate

Prepared from α-(4-methyl-phenyl)-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 34% of theory.

M.p. 150°-152° C.

Calculated: C—74.68%; H—7.44%; N—5.44%. Found: C—74.71%; H—7.51%; N—5.29%.

(w) Ethyl 2-ethoxy-4-[N-(α-phenyl-2-pyrrolidino-benzyl)aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-pyrrolidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 45% of theory.

M.p. 85°-87° C.

Calculated: C—74.05%; H—7.04%; N—5.76%. Found: C—73.95%; H—7.07%; N—5.70%.

(x) Methyl 2-methoxy-4-[N-(2-hexamethyleneimino-α-phenylbenzyl)aminocarbonylmethyl]-benzoate

Prepared from 2-hexamethyleneimino-α-phenyl-benzylamine and 3-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 45% of theory.

M.p. 181°-182° C.

Calculated: C—74.05%; H—7.04%; N—5.74%. Found: C—74.09%; H—6.62%; N—5.74%.

(y) Ethyl 2-ethoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)aminocarbonylmethyl]-benzoate

Prepared from 2-hexamethyleneiminoα-phenyl-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 41% of theory.

M.p. 140°-141° C.

Calculated: C—74.68%; H—7.44%; N—5.44%. Found: C—74.46%; H—7.62%; N—5.45%.

(z) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl-}aminocarbonylmethyl]-toluene

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-methyl-phenylacetic acid.

Yield: 55% of theory.

M.p. 107°-108° C.

Calculated: C—76.43%; H—8.88%; N—6.86%. Found: C—76.38%; H—8.99%; N—6.97%.

(aa) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-heptyl}aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-heptylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 79% of theory.

M.p. 101°-104° C.

Calculated: C—73.19%; H—8.72%; N—5.51%. Found: C—73.00%; H—8.90%; N—5.28%.

EXAMPLE 2

Ethyl
(+)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl-}aminocarbonylmethyl]-benzoate

0.90 g (3.57 mmol) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid and 0.61 g (3.73 mmol) of N,N'-carbonyldiimidazole are refluxed for 5 hours in 9 ml of absolute tetrahydrofuran. Then a solution of 0.85 g (3.67 mmol) of (+)-1-(2-piperidino-phenyl)-1-butylamine (ee=94.2) in 9 ml of absolute tetrahydrofuran is added and the mixture is refluxed for 3 hours. It is concentrated in vacuo and the evaporation residue is distributed between chloroform and water. The organic phase is dried, filtered and evaporated in vacuo. The evaporated extract is purified by column chromatography on silica gel (toluene/acetone=10.1).

Yield: 0.85 g (51.2% of theory).

M.p. 118°-119° C. (petroleum ether/toluene=50/2).

Calculated: C—72.07%; H—8.21%; N—6.00%. Found: C—72.43%; H—8.34%; N—6.00%.

Specific rotation: $[\alpha]_D^{20} = +7.1°$ (c=1.06 in methanol).

The following compounds were obtained analogously to Example 2:

(a) Methyl 3-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 2-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 89% of theory.

M.p. 102°-105° C.

Calculated: C—71.20%; H—7.81%; N—6.39%. Found: C—71.20%; H—8.02%; N—6.27%.

(b) Ethyl 3-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 73% of theory.

M.p. 136°-138° C.

Calculated: C—72.07%; H—8.21%; N—6.00%. Found: C—72.50%; H—8.33%; N—5.95%.

(c) Ethyl 3-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(4-methyl-2-piperidino-phenyl)-1-butylamine and 2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 61% of theory.

M.p. 108°-110° C.

Calculated: C—72.46%; H—8.39%; N—5.83%. Found: C—72.50%; H—8.46%; N—5.92%.

(d) Ethyl 3-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(6-methyl-2-piperidino-phenyl)-1-butylamine and 2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Yield: 90% of theory.

M.p. <20° C.

Calculated: C—72.46%; H—8.39%; N—5.83%. Found: C—72.86%; H—8.20%; N—5.50%.

(e) Methyl 3-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 2-methoxy-4-methoxycarbonyl-phenylacetic acid.

Yield: 86% of theory.
M.p. 144°-148° C.
Calculated: C—73.70%; H—6.83%; N—5.93%.
Found: C—73.70%; H—6.85%; N—5.84%.

(f) Ethyl 3-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzylamine and 2-ethoxy-4-ethoxycarbonyl-phenylacetic acid.
Yield: 77% of theory.
M.p. 112°-115° C.
Calculated: C—74.37%; H—7.25%; N—5.60%.
Found: C—74.69%; H—7.29%; N—5.75%.

EXAMPLE 3

Ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

A solution of 4.7 g (20 mmol) of ethyl 2-ethoxy-4-cyanomethyl-benzoate and 5.3 g (20 mmol) of α-phenyl-2-piperidino-benzyl alcohol in 30 ml of O-dichlorobenzene was added dropwise at 23°-25° C. to a mixture of 30 ml of concentrated sulfuric acid and 30 ml of o-dichlorobenzene. The mixture was stirred for 2 hours at room temperature. Then, the o-dichlorobenzene phase was separated, and the residue was added to ice. After the aqueous mixture had been made alkaline with a soda solution, it was extracted with chloroform. The extracts were dried over magnesium sulfate and concentrated by evaporation. The residue was triturated with petroleum ether (30°-60°), filtered off and purified on silica gel (toluene/ethylacetate=5:1) by column chromatography.
Yield: 5.6 g (56% of theory).
M.p. 150°-151° C.
Calculated: C—74.37%; H—7.25%; N—5.60%.
Found: C—74.59%; H—7.41%; N—5.45%.

The following compounds were obtained by a procedure analogous to that described in Example 3:

(a) Methyl 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzyl alcohol and methyl 4-cyanomethyl-2-methoxy-benzoate.
Yield: 34% of theory.
M.P. 189°-191° C.
Calculated: C—73.70%; H—6.83%; N—5.93%.
Found: C—73.63%; H—7.05%; N—5.95%.

(b) 2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from α-phenyl-2-piperidino-benzyl alcohol and 2-ethoxy-4-cyanomethyl-benzoic acid.
Extraction at pH 5.
Yield: 47% of theory.
M.p. 154°-155° C.
Calculated: C—74.70%; H—6.83%; N—5.93%.
Found: C—73.61%; H—6.72%; N—5.65%.

(c) 2-Methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from α-phenyl-2-piperidino-benzyl alcohol and 4-cyanomethyl-2-methoxy-benzoic acid.
Extraction at pH 5.
Yield: 30% of theory.
M.p. 202°-204° C.
Calculated: C—73.34%; H—6.59%; N—6.11%.
Found: C—73.17%; H—6.41%; N—6.05%.

(d) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-butanol and ethyl-2-ethoxy-4-cyanomethyl benzoate.
Yield: 5% of theory.
M.p. 112°-114° C.
Calculated: C—72.07%; H—8.21%; N—6.00%.
Found: C—72.29%; H—8.46%; N—6.31%.

(e) Methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-ethanol and methyl 4-cyanomethyl-2-methoxy-benzoate.
Yield: 18% of theory.
M.p. 83°-85° C.
Calculated: C—70.22%; H—7.37%; N—6.82%.
Found: C—70.60%; H—7.29%; N—6.97%.

(f) 2-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoic acid

Prepared from 1-(2-piperidino-phenyl)-1-ethanol and 4-cyanomethyl-2-methoxy-benzoic acid.
Extraction at pH 5.5.
Yield: 21% of theory.
M.p. 118°-120° C.
Calculated: m/e=396 Found: m/e=386.

(g) Ethyl 2-ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidinobenzyl)aminocarbonylmethyl]-benzoate

Prepared from 4-methyl-α-phenyl-2-piperidino-benzyl alcohol and ethyl 2-ethoxy-4-cyanomethyl-benzoate.
Yield: 45% of theory.
M.p. 124°-125° C.
Calculated: C—74.68%; H—7.44%; N—5.44%.
Found: C—74.81%; H—7.56%; N—5.32%.

(h) Methyl 2-methoxy-4-[N-{α-(4-chloro-phenyl)-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-(4-chlorophenyl)-2-piperidino-benzyl alcohol and methyl 2-methoxy-4-cyanomethyl-benzoate.
Yield: 47% of theory.
M.p. 176°-178° C.
Calculated: C—68.70%; H—6.17%; N—5.53%; Cl—6.99%. Found: C—69.05%; H—5.93%; N—5.76%; Cl—7.10%.

(i) Ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzyl alcohol and ethyl 4-cyanomeethyl-2-hydroxy-benzoate.
Yield: 78% of theory.
M.p. 172°-174° C.
Calculated: C—73.70%; H—6.83%; N—5.93%.
Found: C—73.80%; H—6.81%; N—5.83%.

(k) n-Propyl 2-n-propoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from α-phenyl-2-piperidino-benzyl alcohol and n-propyl 4-cyanomethyl-2-n-propoxy benzoate.
Yield: 52% of theory.
M.p. 119°-120° C.
Calculated: C—74.97%; H—7.63%; N—5.30%.
Found: C—74.91%; H—7.72%; N—5.25%.

EXAMPLE 4

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

A mixture of 2 g (4.3 mmols) of ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate and 5.3 ml of 1N sodium hydroxide solution in 20 ml of ethanol was stirred for 3 hours at 60° C., then neutralized with 5.3 ml of 1N hydrochloric acid, and the ethanol was evaporated in vacuo. The residue

was taken up in a mixture of ethyl acetate and water, and the organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was crystallized from petroleum ether with the addition of ethanol.

Yield: 1.3 g (69% of theory).

M.p. 88°-90° C.

Calculated: C—71.21%; H—7.81%; N—6.39%. Found: C—71.62%; H—7.73%; N—6.54%.

The following compounds were obtained by a procedure analogous to that described in Example 4:

(a) 2-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoic acid × 0.67 H_2O

Prepared from methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoate.

Yield: 60% of theory.

M.p. 116°-120° C.

Calculated: C—67.62%; H—7.07%; N—6.85%. Found: C—67.60%; H—6.87%; N—6.55%.

(b) 2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate.

Yield: 89% of theory.

M.p. 155°-156° C.

Calculated: C—73.70%; H—6.83%; N—5.93%. Found: C—73.60%; H—6.96%; N—6.12%.

(c) 2-Methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl)-benzoic acid

Prepared from methyl 2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 68% of theory.

M.p. 202°-204° C.

Calculated: C—73.34%; H—6.59%; N—6.11%. Found: C—73.60%; H—6.77%; N—6.20%.

(d) 2-Ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate.

Yield: 74% of theory.

M.p. 115°-118° C.

Calculated: C—65.42%; H—6.81%; N—6.10%; Cl—7.72%. Found: C—65.54%; H—6.94%; N—5.81%; Cl—7.89%.

(e) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoate.

Yield: 73% of theory.

M.p. 81°-83° C.

Calculated: C—70.73%; H—7.60%; N—6.60%. Found: C—70.90%; H—7.47%; N—6.77%.

(f) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl}-aminocarbonylmethyl]-benzoate.

Yield: 92% of theory.

M.p. 82°-85° C.

Calculated: C—71.65%; H—8.02%; N—6.19%. Found: C—71.45%; H—8.01%; N—6.13%.

(g) 2-Ethoxy-4-[N-{1-(2-pyrrolidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-pyrrolidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 77% of theory.

M.p. 120°-123° C.

Calculated: C—70.73%; H—7.60%; N—6.60%. Found: C—70.71%; H—7.44%; N—6.33%.

(h) 2-Ethoxy-4-[N-{1-(2-(4-methyl-piperidino)-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-(4-methyl-piperidino)-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 71% of theory.

M.p. 83°-85° C.

Calculated: C—71.65%; H—8.02%; N—6.19%. Found: C—71.60%; H—7.94%; N—6.09%.

(i) 2-Ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 81% of theory.

M.p. 101°-105° C.

Calculated: C—71.65%; H—8.02%; N—6.19%. Found: C—71.31%; H—7.79%; N—6.18%.

(k) 2-Ethoxy-4-[N-{1-(6-chloro-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(6-chloro-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 82% of theory.

M.p. 133°-136° C.

Calculated: C—66.02%; H—7.03%; N—5.92%; Cl—7.50%. Found: C—66.48%; H—7.47%; N—5.98%.

(l) 2-Ethoxy-4-[N-{1-(4-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(4-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 81% of theory.

M.p. 98°-100° C.

Calculated: C—69.21%; H—7.74%; N—5.98%. Found: C—69.12%; H—7.62%; N—5.78%.

(m) 2-Ethoxy-4-[N-{1-(5-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(5-methoxy-2-piperidino-phenyl)-1-butyl}-aminocarbonylmetehyl]-benzoate.

Yield: 74% of theory.

M.p. 145°-148° C.

Calculated: C—69.21%; H—7.74%; N—5.98%. Found: C—69.00%; H-7.65%; N—5.89%.

(n) 2-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 86% of theory.

M.p. 140°-143° C.

Calculated: C—70.73%; H—7.60%; N—6.60%. Found: C—70.49%; H—7.58%; N—6.31%.

(o) 2-n-Propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from n-propyl 2-n-propoxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 89% of theory.

M.p. 128°-132° C.

Calculated: C—71.65%; H—8.02%; N—6.19%. Found: C—71.40%; H—7.90%; N—6.47%.

(p) 2-Ethoxy-4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid × 0.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-5-chloro-2-piperidinobenzyl)-aminocarbonyl-methyl]-benzoate.

Yield: 93% of theory.

M.p. 153°-155° C.

Calculated: C—62.79%; H—6.41%; N—6.36%; Cl—8.06%. Found: C—63.21%; H—6.34%; N—5.89%; Cl—8.46%.

(g) 2-Ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 77% of theory.

M.p. 108°-109° C.

Calculated: C—69.68%; H—7.12%; N—7.07%. Found: C—70.00%; H—7.99%; N—7.31%.

(r) 2-Hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-hydroxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 61% of theory.

M.p. 136°-138° C.

Calculated: C—70.22%; H—7.37%; N—6.82%. Found: C—70.40%; H—7.64%; N—6.60%.

(s) 2-Isopropoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-isopropoxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 67% of theory.

M.p. 115°-118° C.

Calculated: C—71.65%; H—8.02%; N—6.19%. Found: C—71.94%; H—7.96%; N—6.04%.

(t) 2-Allyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmetehyl]-benzoic acid

Prepared from ethyl 2-allyloxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 92% of theory.

M.p. 110°-112° C.

Calculated: C—71.97%; H—7.61%; N—6.22%. Found: C—71.90%; H—7.62%; N—6.21%.

(u) 2-Benzyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-benzyloxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 95% of theory.

M.p. 161°-163° C.

Calculated: C—74.37%; N—7.25%; N—5.60%. Found: C—74.40%; N—7.44%; N—5.64%.

(v) (+)-2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl (+)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]benzoate.

Yield: 81% of theory.

M.p. 122°-123° C.

Calculated: C—71.21%; H—7.81%; N—6.39%. Found: C—71.19%; H—7.77%; N—6.29%.

Specific rotation $[\alpha]_D^{20} = 4.75°$ (c = 1.03 in methanol).

(w) 3-Methoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 3-methoxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 64% of theory.

M.p. 188°-191° C.

Calculated: C—70.73%; H—7.60%; N—6.60%. Found: C—70.88%; H—7.56%; N—6.59%.

(x) 3-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 3-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 79% of theory.

M.p. 159°-165° C.

Calculated: C—71.21%; H—7.81%; N—6.39%. Found: C—71.32%; H—7.62%; N—6.24%.

(y) 3-Ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 3-ethoxy-4-[N-{1-(4-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 71% of theory.

M.p. 186°-188° C.

Calculated: C—71.65%; H—8.02%; N—6.19%. Found: C—71.70%; H—7.86%; N—6.26%.

(z) 3-Ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 3-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 65% of theory.

M.p. 174°-176° C.

Calculated: C—71.65%; H-8.02%; N-6.19%. Found: C—72.00%; H—8.10%; N—5.91%.

(aa) 2-Ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidine-benzyl)aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 41% of theory.

M.p. 127°-129° C.

Calculated: C—74.05%; H—7.04%; N—5.76%. Found: C—73.80%; H—7,09%; N—5.74%.

(ab) 2-Ethoxy-4-[N(6-methyl-α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 40% of theory.

M.p. 118°-121° C.

Calculated: C—74.05%; H—7,04%; N—5.76%. Found: C—73.71%; H—6.92%; N—5.76%.

(ac) 2-Ethoxy-4-[N-{α-(4-methyl-phenyl)-2-piperidino-benzyl}aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{α-(4-methyl-phenyl)-2-piperidino-benzyl}-aminocarbonylmethyl]-benzoate.

Yield: 94% of theory.

M.p. 148°-151° C.

Calculated: C—74.05%; H—7.04%; N—5.76%. Found: C—74.20%; H—7.15%; N—5.81%.

(ad) 2-Methoxy-4-[N-{α-(4-chloro-phenyl)-2-piperidino-benzyl}aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-{α-(4-chloro-phenyl)-2-piperidino-benzyl}-aminocarbonylmethyl]-benzoate.

Yield: 77% of theory.

m.p. 177°-180° C.

Calculated: C—68.21%; H—5.03%; N—5.68%; Cl—7.19%. Found: C—68.10%; H—5.78%; N—5.53%; Cl—7.43%.

(ae) 2-Ethoxy-4-[N-(α-phenyl-2-pyrrolidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(α-phenyl-2-pyrrolidinobenzyl)-aminocarbonylmethyl]-benzoate.

Yield: 67% of theory.

M.p. 141°-143° C.

Calculated: C—73.34%; H—6.59%; N—6.11%. Found: C—73.33%; H—6.74%; N—6.02l %.

(af) 2-Methoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 2-methoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 90% of theory.

M.p. 154°-156° C.

Calculated: C—73.70%; H—6.83%; N—5.93%. Found: C—73.70%; H—7.00%; N—5.95%.

(ag) 2-Ethoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocrbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-(2-hexamethyleneimino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 75% of theory.

M.p. 139°-141° C.

Calculated: C—74.05%; H—7.04%; N—5.76%. Found: C—73.90%; H—7.14%; N—5.78%.

(ah) 2-Hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate by hydrolysis with 4 equivalents of 1N sodium hydroxide in ethanol/dioxane.

Yield: 35% of theory.

M.p. 222°-224° C.

Calculated: C—72.95%; H—6.35%; N—6.30%. Found: C—73.00%; H—6.64%; N—6.28%.

(ai) 2-n-Propoxy-4-[N-(α-phenyl-2-piperidino-benzyl-)aminocarbonylmethyl]-benzoic acid

Prepared from n-propyl 2-n-propoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 41% of theory.

M.p. 168°-170° C.

Calculated: C—74.05%; H—7.04%; N—5.76%. Found: C—74.20%; H—7.19%; N—5.57%.

(ak) 2-Allyloxy-4-[N-(α-phenyl-2-piperidino-benzyl-)aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-allyloxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 69% of theory.

M.p. 172°-172° C.

Calculated: C—74.35%; H—6.66%; N—5.78%. Found: C—74.11%; H—6.50%; N—5.74%.

(al) 2-Benzyloxy-4-[N-(α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-benzyloxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 72% of theory.

M.p. 214°-215° C.

Calculated: C—76.38%; H—6.41%; N—5.24%. Found: C—76.18%; H—6.39%; N—5.36%.

(am) (−)-2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoic acid

Prepared from ethyl (−)-2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 89% of theory.

M.p. 90°-95° C.

Calculated: C—73.70%; H—6.83%; N—5.93%. Found: C—73.59%; H—6.81%; N—5.83%.

Specific rotation: $[\alpha]_D^{20} = -2.2°$ (c = 1 in methanol).

(an) 3-Methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared from methyl 3-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 72% of theory.

M.p. 220°-221° C.

Calculated: C—73.34%; H—6.59%; N—6.11%. Found: C—73.36%; H—6.46%; N—5.86%.

(ao) 3-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl-)aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 3-ethoxy-4-[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate.

Yield: 70% of theory.

M.p. 199°-201° C.

Calculated: C-73.70%; H-6.83%; N-5.93%. Found: C—73.50%; H—6.74%; N—5.94%.

(ap) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-heptyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4[N-{1-(2-piperidino-phenyl)-1-heptyl}-aminocarbonylmethyl]-benzoate.

Yield: 88% of theory.

M.p. 71°-73° C.

Calculated: C—72.47%; H—8.39%; N—5.83%. Found: C—72.28%; H—8.56%; N—5.82%.

EXAMPLE 5

Sodium salt of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl-}aminocarbonylmethyl]-benzoic acid x 1.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoate analogous to Example 4. After purification by column chromatography the evaporation residue was dissolved in ethanol and mixed with 1 equivalent of 1N sodium hydroxide. By evaporation in vacuo and trituration with acetone, the crystalline sodium salt was obtained.

Yield: 76% of theory.

M.p. 242°-244° C.

Calculated: C—62.73%; H—7.01%; N—6.01%. Found: C—62.74%; H—7.17%; N—6.05%.

The following compounds were obtained by a procedure analogous to that described in Example 5;

(a) Sodium salt of 2-ethoxy-4-[N-{1-(4-methyl-2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid x 0.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-{1-(4-methyl2-piperidion-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 72% of theory.

M.p. 255°-260° C.

Calculated: C—67.06%; H—7.50%; N—5.79%. Found: C—66.94%; H—7.28%; N—5.50%.

(b) Sodium salt of 2-ethoxy-4[N-{1-(6-methyl-2-piperidinophenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid × 2.5 H_2O

Prepared from ethyl 2-ethoxy-4-[N-{1-(6-methyl-2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 81% of theory.

M.p. 232°-240° C.

Calculated: C—62.39%; H—7.75%; N—5.39%. Found: C—62.22%; H—7.46%; N—5.61%.

(c) Sodium salt of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate.

Yield: 87% of theory.

M.p. 250°-258° C.
Calculated: C—67.79%; H—7.22%; N—6.08%. Found: C—67.60%; H—7.37%; N—6.04%.
(d) Sodium salt of 2-ethoxy-4-(α-phenyl-2-piperidinobenzyl)aminocarbonylmethyl]-benzoic acid
Prepared from ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate.
Yield: 89% of theory.
M.p. 233°-235° C.
Calculated: C—70.42%; H—6.32%; N—5.67%. Found: C—70.20%; H—6.41%; N—5.49%.

EXAMPLE 6

Ethyl
2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

1 ml (10.4 mmols) of boron tribromide was added dropwise at −20° C. under anhydrous conditions to a stirred solution of 2 g (4 mmols) of ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate in 20 ml of 1,2-dichloroethane. The mixture was allowed to reach room temperature and was then stirred for 17 hours. It was then poured into ethanol, evaporated in vacuo, ice was added, and the resulting mixture was taken up in a mixture of chloroform and water. The organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (toluene/ethyl acetate=5/1).
Yield: 0.37 g (21% of theory).
M.p. 172°-173° C.
Calculated: C—73.70%; H—6.83%; N—5.93%. Found: C—73.95%; H—7.05%; N—6.12%.
The following compounds were obtained by a procedure analogous to that described in Example 6:
(a) 2-Hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl-)aminocarbonylmethyl]-benzoic acid
Prepared from 2-ethoxy-4[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid.
Yield: 40% of theory.
M.p. 221°-223° C.
Calculated: C—72.95%; H—6.35%; N—6.30%. Found: C—72.68%; H—6.45%; N—6.49%.
(b) Ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}aminocarbonylmethyl]-benzoate
Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.
Yield: 19% of theory.
M.P. 132°-134° C.
Calculated: C—71.21; H—7.81; N—6.39; Found: C—71.43; H—7.91; N—6.55;
(c) 2-Hydroxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl-)aminocarbonylmethyl]-benzoic acid
Prepared from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 42% of theory.
M.P. 136°-137° C.
Calculated: C—70.22%; H—7.37%; N—6.82%. Found: C—70.19%; H—7.39%; N—6.99%.

EXAMPLE 7

Tert.butyl
2-ethoxy-4[N-{1-(2-piperidino-phenyl)-1-butyl-}aminocarbonylmethyl]-benzoate

A mixture of 1.9 g (9.6 mmols) of N,N'-dicyclohexyl-carbodiimide, 1.06 ml (11.2 mmols) of absolute tert-butanol and 0.020 g (0.20 mmol) of copper(I) chloride was stirred for 60 hours at room temperature. Then, 6.6 ml of methylene chloride were added, and the resulting solution was added dropwise to a solution of 0.44 g (1 mmol) of 2-ethyoxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid in 15 ml of methylene chloride. After 60 hours' stirring at 20° C., the precipitate which had formed was filtered off, washed with methylene chloride, and the methylene chloride solution was evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (chloroform/ethyl acetate=9/1).
Yield: 0.30 g (60% of theory).
M.p. 74°-77° C. (from petroleum ether).
Calculated: C—72.84%; H—8.56%; N—5.66%. Found: C—73.00%; H—8.56%; N—5.79%.

EXAMPLE 8

Ethyl
2-benzyloxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

0.10 g (2.3 mmols) of sodium hydride (55% in oil) was added to a solution of 1.1 g (2.3 mmols) of ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 10 ml of anhydrous dimethylformamide and the resulting mixture was stirred for half an hour at room temperature. Then, a solution of 0.27 ml (2.3 mmols) of benzyl bromide in 5 ml of anhydrous dimethylformamide was added dropwise, and the resulting mixture was stirred for 5 hours at room temperature. It was then evaporated in vacuo, the residue was taken up in a mixture of dilute sodium hydroxide and chloroform, and the organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was recrystallized from acetonitrile.
Yield: 0.9 g (69.5% of theory).
M.p. 156°-157° C.
Calculated: C—76.84% H—6.81%; N—4.98%. Found: C—76.94%; H—6.95%; N—4.87%.
The following compounds were obtained by a procedure analogous to that described in Example 8:
(a) Ethyl 2-allyloxy-4[N-(α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoate
Prepared from ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate, using allyl bromide.
Yield: 46% of theory.
M.p. 117°-119° C.
Calculated: C—74.97%; H—7.08%; N—5.47%. Found: C—74.90%; H—7.14%; N—5.38%.
(b) Ethyl 2-isopropoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}aminocarbonylmethyl]-benzoate
Prepared from ethyl 2-hydroxy-4-[N-{1-(2-piperidinophenyl)-1-butyl}-aminocarbonylmethyl]-benzoate, using 1.5 equivalents of isopropyl bromide at 150° C.
Yield: 56% of theory.
M.p. 98°-99° C.
Calculated: C—72.47%; H—8.39%; N—5.83%. Found: C—72.60%; H—8.60%; N—5.75%.
(c) Ethyl 2-allyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}aminocarbonylmethyl]-benzoate
Prepared from ethyl 2-hydroxy-4-[N-{1-(2-piperidinophenyl) -1-butyl}-aminocarbonylmethyl]-benzoate, using allyl bromide.
Yield: 72% of theory.
M.p. 105°-106° C.

Calculated: C—72.77%; H—8.00%; N—5.85%.
Found: C—72.90%; H—7.90%; N—5.87%.

(d) Ethyl 2-benzyloxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-hydroxy-4[N-{1-(2-piperidinophenyl) -1-butyl}-aminocarbonylmethyl]-benzoate, using benzyl bromide.

Yield: 80% of theory.

M.p. 135°-136° C.

Calculated: C—74.97%; H—7.63%; N—5.30%.
Found: C—75.20%; H—7.78%; H—5.59%.

EXAMPLE 9

n-Propyl
2-n-propoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from 2-hydroxy-4-(N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid analogous to Example 8, using 2equivalents of sodium hydride and 2 equivalents of n-propyl bromide.

Yield: 45% of theory.

M.p. 118°-120° C.

Calculated: C—74.97%; H—7.63%; N—5.30%.
Found: C—75.20% H—7.80%; N—5.41%.

The following compound was obtained by a procedure analogous to that described in Example 9;

(a) n-Propyl 2-n-propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from n-propyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

Yield: 39% of theory.

M.p. 89-°90° C.

Calculated: C—72:84%; H—8.56%; N—5.66%.
Found: C—72.95%; H—8.77%; N-5.59%.

EXAMPLE 10

Ethyl
2-ethoxy-4-[N-(2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

1.0 g (2.18 mmols) of ethyl 2-ethoxy4-[N-(5-chloro-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate was hydrogenated in 20 ml of ethanol with 0.5 g of 10% palladium-on-charcoal at 50° C. under 1 bar of hydrogen for 45 minutes. The reaction mixture was filtered through diatomaceous earths, the filtrate was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (chloroform/methanol-10/1).

Yield: 0.71 g (77% of theory).

M.p. 83°-84° C. (from petroleum ether).

Calculated: C—70.73%; H—7.60%; N—6.60%.
Found: C—70.89%; H—7.66%; N—6.76%.

The following compound was obtained by a procedure analogous to that described in Example 10:

(a) Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-{1-(5-chloro-2-piperidino-phenyl)-1-propyl}-aminocarbonylmethyl]-benzoate.

Yield: 74% of theory.

M.p. 115°-117° C.

Calculated: C—71.65%; H—8.02%; N—6.19%.
Found: C—71.47%; H—8.11%; N—6.25%.

EXAMPLE 11

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid (form A)

(a) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoic acid.

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoate.

Yield: 85% of theory.

M.p. 110°-113° C.

Calcuated: C—71.97%; H—7.61%; N—6.22%.
Found: C—71.92%; H—7.80%; N—5.98%.

(b) 0.21 g (0.39 mmol) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoic acid were hydrogenated in 10 ml of absolute ethanol with 0.10 g of 10palladium-on-charcoal at 50° C. and a pressure of 1 bar of hydrogen for 7 hours. The reaction mixture was then filtered through diatomaceous earth, the reaction filtrate was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (chloroform/methanol = 10/1).

Yield: 0.10 g (47% of theory).

M.p. 90°-92° C. (recrystallized from acetone/petroleum ether).

Calculated: C—71.65% H—8.02%; N—6.19%.
Found: C—71.50%; H—8.12%; N—6.45%.

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, is also obtained in other solid forms when it is crystallized from other solvents or mixtures of solvents. Form (B), which has a melting point of 140° to 142° C., is obtained by crystallization from an ethanol/water mixture. The foamy form (C), which has a melting point range from 75° to 85° C., is obtained from the 1:1 methanol adduct (melting point: 85° to 90° C.), which occurs upon crystallization from methanol, by heating at 60° C. in vacuo (5 Torr) over phosphorous pentoxide, whereby the methanol is removed.

In the dissolved state those forms are identical, as is evident from the corresponding solution spectra, for instance the IR-spectra in methylene chloride shown in FIGS. 1, 2 and 3 of the attached drawings. However, in the solid state, the three forms differ in their melting characteristics and their solid spectra, for instance as shown by the corresponding IR-KBr-spectra in FIGS. 4, 5 and 6 of the attached drawings.

In order to measure infra-red absorption, forms (A), (B) and (C) were dissolved in methylene chloride (40 mg of substance per ml of methylene chloride), or intimately triturated with potassium bromide and then compressed hydraulically to form a tablet (approx. 1 mg of substance/300 mg of KBr).

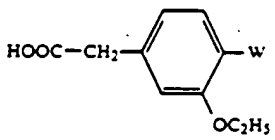
In the case of the solutions, the IR-spectra were measured with an IR-spectrometer (Perkin Elmer Type 299) in a cell of sodium chloride (layer thickness 0.2 mm) by comparison with a pure methylene chloride solution and, in the case of the potassium bromide tablets, with an IR-spectrometer (Perkin Elmer Type 298) by comparison with air.

The three solid forms can be conveyed into one another by suitable recrystallization and drying. Thus, the low-melting-point form (A) is obtained by recrystallizing the high-melting-point form (B) from acetone/petroleum ether and the high-melting-point form (B) is obtained by recrystallizing the low-melting-point form

(A) from ethanol/water. By recrystallizing the high-melting-point form (B) from methanol, a 1:1 adduct with methanol is obtained, and from this the foamy form (C) is obtained by removing the methanol.

Irrespective of the particular process which is used to synthesize 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, therefore, the heat-melting-point or low-melting-point or foamy form can be obtained, as desired, by a suitable choice of solvent or mixture of solvents during crystallization and by suitable drying. This is important in the practical use of the solid forms, whether or not they are accompanied by galenic excipients in pharmaceutical compositions, particularly for lowering blood sugar in the treatment of Type II diabetes; this is because different solid forms may have different shelf lives and/or different absorption characteristics in vivo and may thus give a different pattern of biological activity.

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid may be obtained by the methods described hereinabove, but preferably by reacting 3-methyl-1-(2-piperidino-phenyl)-1-butylamine with a compound of the formula



(XI)

wherein W is carboxyl or carboxyl protected by a protective group or with a reactive derivative thereof, optionally prepared in the reaction mixture, followed, if necessary, by removal of the protective group, and the solid forms (B) and (C) are obtained by suitable subsequent crystallization, suitable final recrystallization and/or drying.

Examples of reactive derivatives of a compound of the formula XI include the esters such as the methyl, ethyl and benzyl esters thereof, the thioesters such as the methylthio and ethylthioesters, the halides such as the acid chloride, the anhydrides and imidazolides thereof.

The reaction is advantageously carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an acid-activating agent or a dehydrating agent, for instance in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or in the presence of an amino group activating agent, such as phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a teritary organic base such as triethylamine or pyridine, which may simultaneously serve as solvent, at temperatures between −25° and 250° C., but preferably at temperatures between −10° C. and the boiling point of the solvent which is used. The reaction may also be carried out without a solvent, and any water formed during the reaction may be removed by azeotropic distillation, for instance by heating with toluene, using a water trap, or by adding a drying agent such as magnesium sulfate or a molecular sieve.

The subsequent removal of the protective group is preferably carried out by hydrolysis, either in the presence of an acid such as hydrochloric, sulfuric, phosphoric or trichloroacetic acid, or in the presence of a base such as sodium hydroxide or potassium hydroxide, in a suitable solvent such as water, methanol, methanol/water, ethanol, ethanol/water, water/isopropanol or water/dioxane at temperatures between −10° and 120° C., for instance at temperatures betwen room temperature and the boiling point of the reaction mixture.

A tert.butyl protective group may also be removed thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane, and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulfonic, sulfuric, phosphoric or polyphosphoric acid.

Moreover, a benzyl protective group may also be removed by hydrogenation in the presence of a hydrogenation catalyst such as palladium-on-charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide.

The subsequent crystallization is carried out in sutu from the reaction mixture containing ethanol/water or, as a final recrystallization, by dissolving the reaction product in a mixture of ethanol and water, optionally while heating, and cooling, optionally accompanied by trituration and/or seeding (form B), or by dissolving the reaction product in acetone and adding petroleum ether (form A), or by dissolving the reaction product, optionally while heating in methanol, subsequent cooling of the solution accompanied by trituration and/or seeding, and heating the isolated solid methanol adducts, preferably in vacuo, in the presence of a drying agent such as phosphorus pentoxide (form C).

Like the other compounds of the formula I, solid forms (A), (B) and (C) of 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid may also be converted into their salts, particularly their non-toxic, pharmacologically acceptable table salts with inorganic or organic acids or bases. Suitable acids for this purpose are, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, lactic citric, trataric, succinic, maleic or fumaric acid, and suitable bases are sodium hydroxide, potassium hydroxide, calcium hydroxide, cyclohexylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine or lysine.

The melting points in Examples 12-16 were determined in an Electrothermal ® melting point apparatus with visual observation of the sample of product in a capillary tube fused at one end.

EXAMPLE 12

Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoate

3 g (11.9 mmols) of 3-ethoxy-4-ethoxycarbonylphenylacetic acid, 3.7 g (14.3 mmols) of triphenylphosphine, 3.3 ml (23.8 mmols) of triethylamine and 1.15 ml (11.9 mmols) of carbon tetrachloride were added successively to a solution of 2.9 g (11.9 mmols) of 3-methyl-1-(2-piperidino-phenyl)-1-butylamine in 29 of acetonitrile. The mixture was then stirred for 15 hours at room temperature, the solvent was removed in vacuo, and the residue was taken up in a mixture of ethyl acetate and

water. The organic phase was dried over sodium sulfate, filtered and concentrated by evaporation in vacuo. The evaporation residue was purified by column chromatography on silaca gel (toluene/acetone = 10/1).

Yield: 4.9 g (85% of theory).

M.p. 143°–145° C. (petroleum ether).

Calculated: C-72.47%; H-8.39%; N-5.83%.

Found: C-72.37%; H-8.45%; N-6.07%.

EXAMPLE 13

High-melting-point form (B) of 2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

A mixture of 4.7 g (9.7 mmols) of ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate and 14.7 ml of 1N sodium hydroxide was stirred in 47 ml of ethanol for 2 hours at 60° C., then neutralized with 14.7 ml of 1N hydrochloric acid and cooled to 0° C. The mixture was filtered to remove the precipitated colorless crystals, and the crystals were washed with ice water and with a little ice cold ethanol and then dried at 100° C./1 Torr.

Yield: 3.9 g (88% of theory).

M.p. 140°–142° C.

Calculated: C-71.65%; H-8.02%; N-6.19%. Found: C-71.90%; H-8.08%; N-6.34%.

Upon further recrystallization from ethanol/water (2/1) the melting point remained constant.

EXAMPLE 14

Low-melting-point form (A) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

1.0 g of the high-melting-point form (B) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonyl-methyl]-benzoic acid was dissolved at room temperature in 5 ml of acetone, and 5 of petroleum ether (m.p. 60°–70° C.) were added. Upon trituration, crystallization gradually set in. The same quantity of petroleum ether was added again, and after crystallization had ended, the mixture was filtered. The crystals were washed with petroleum ether, and the almost colorless crystals were dried for 2 hours at 60° C./0.1 Torr.

Yield: 0.7 g

M.p. 95°–98° C. (clear beginning at 135° C.).

Calculated: C-71.65%; H-8.02%; N-6.19%. Found: C-71.80%; H-8.04%; N-5.92%.

The IR-spectra for this form (see FIGS. 1 and 4) are identical to the IR-spectra for the form (A), melting point 90°–92° C., described in Example 11(b) above.

EXAMPLE 15

High-melting-point form (B) of 2-ethoxy-4[N-{1-2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

1.0 g of the low-melting-point form (A) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-amino-carbonylmethyl[-benzoic acid was dissolved in 10 ml of ethanol/water (2/1) while heating over a steam bath. The solution was then cooled to 0° C., whereupon crystallization began. The mixture was filtered, and the residue was washed with a little ice-cold ethanol and dried at 100° C./1 Torr.

Yield: 0.8 g.

M.p. 140°–142° C.

EXAMPLE 16

Foamy form (C) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

1.5 g of the high-melting -point form (B) of 2--ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonyl-methyl]-benzoic acid was dissolved in 5 ml of methanol while heating. The solution was then cooled to 0° C. with trituration. The crystals precipitated thereby were separated by filtration, washed with a little cold methanol, and dried for 2 hours at 60° C./0.1 Torr.

Yield of adduct (with $1 \times CH_3OH$): 1.2 g.

M.p. 85°–90° C.

Calculated: ($\times 1CH_3OH$): C-69.39%; H-8.32%; N-5.78%.

Found: C-69.20%; H-8.20%; N-5.92%.

The adduct was converted into the methanol-free foamy form (C) by heating for 24 hours at 60° C./5 Torr over phosphorus pentoxide.

Melting range: 75°–85° C.

Calculated: C-71.65%; H-8.02%; N-6.19%. Found: C-71.82%; H-8.06%; N-6.03%.

EXAMPLE 17

Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-buten-1-yl}-aminocarbonylmethyl]-benzoate, melting point 125°–126° C., which in turn was prepared from (2-piperidino-phenyl)-isobutyl-ketimine and 3-ethoxy-4-ethoxy-carbonyl-phenol-acetic acid analogous to Example 1.

Yield: 51% of theory.

M.p. 139°–141° C.

Calculated: C-72.47%; H-8.39%; N-5.83%. Found: C-72.30%; H-8.20%; N-5.87%.

EXAMPLE 18

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzyl alcohol

A solution of 1.8 g (3.6 mmols) of ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 20 ml of absolute tetrahydrofuran was added dropwise at −5° C. to a mixture of 0.28 g (7.4 mmols) of lithium aluminum hydride and 50 ml of absolute tetrahydrofuran, and the resulting mixture was stirred for 3 hours at 0° C. It was then diluted with absolute ether, and 4N sodium hydroxide was added. The mixture was filtered through diatomaceous earth, the filtrate was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).

Yield: 0.51 g (31% of theory).

M.p. 133°–135° C.

Calculated: C-75.95%; H-7.47%; N-6.11%; Found: C-75.97%; H-7.55%; N-5.95%.

The following compound was obtained by a procedure analogous to that described in Example 18:

(a) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzyl alcohol

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)1-butyl}-aminocarbonylmethyl}-benzoate by

reduction with lithium borohydride in boiling tetrahydrofuran in the presence of 10% of trimethyl borate.

Yield: 68% of theory.

M.p. 112°-115° C.

Calculated: C-73.55%; H-8.55%; N-6.60%. Found: C-73.60%; H-8.38%; N-6.69%.

EXAMPLE 19

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonyl-methyl]-benzaldehyde

A solution of 0.4 g (0.87 mmol) of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzyl alcohol was added dropwise at room temperature to a stirred solution of 0.28 g (1.3 mmols) of pyridinium chlorochromate in 5 ml of chloroform. The reaction mixture was stirred overnight at room temperature, evaporated in vacuo, the residue was mixed with ether, the etheral mixture was filtered, the filtrate was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).

Yield: 0.16 g (40% of theory).

M.p. 154°-156° C.

Calculated: C-76.29%; H-7.06%; N-6.14%. Found: C-76.30%; H-7.15%; N-6.10%

The following compound was obtained by a procedure analogous to that described in Example 19:

(a) 2-Ethoxy-4-[N-{1-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzaldehyde

Prepared from 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzyl alcohol.

Yield: 47% of theory.

M.p. 109°-111° C.

Calculated: C-73.90%; H-8.11%; N-6.63%. Found: C-74.22%; H-8.14%; N-6.73%.

EXAMPLE 20

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzaldehyde

0.67 g (5.6 mmols) of sodium carbonate was heated together with 6 ml of ethylene glycol on an oil bath at 170° C., and then, while rapidly stirring, 0.70 g (1.1 mmols) of N^1-[2-ethoxy-4-{N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl}-benzoyl]-N^2-tosyl-hydrazine were added thereto within a minute; a violent evolution of gas was observed. Then, the mixture was heated for 2 minutes more at 170° C. and then poured immediately over ice. The aqueous mixture was extracted with ether, and the extract was dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 2/1).

Yield: 0.25 g (50% of theory).

M.p. 153°-156° C.

Calculated: C-76.29%; H-7.06%; N-6.14%. Found: C-76.42%; H-7.33%; N-6.28%.

The following compound was obtained by a procedure analogous to that described in Example 20:

(a) 2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzaldehyde

Prepared from N^1-[2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoyl]-N^2-tosyl-hydrazine.

Yield: 51% of theory.

M.p. 108°-111° C.

Calculated: C-73.90%; H-8.11%; N-6.63%. Found: C-73.79%; H-8.29%; N-6.75%.

EXAMPLE 21

Benzyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzoate

0.35 g (0.8 mmol) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid was refluxed together with 0.15 g (0.9 mmol) of N,N'-carbonyldiimidazole in 15 ml of absolute tetrahydrofuran for 2 hours, Then, 1.03 ml (10 mmols) of benzyl alcohol were added, and the mixture was refluxed for 3.5 hours. The reaction mixture was then evaporated in vacuo, and the residue was purified by column chromatography on silica gel (chloroform/acetone = 9/1).

Yield: 0.10 g (23.6% of theory).

M.p. <20° C.

Calculated: Mol peak m/e = 528. Found: Mol peak m/e = 528.

EXAMPLE 22

Ethyl (±)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate and

Ethyl (−)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate

28 mg of ethyl (±)-2-ethoxy-4-N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate were added in 0.02 mg-portions to a chiral phase HPLC column made by the Baker Co., in which (R)-N-3,5-dinitrobenzoyl-phenylglycine was covalently bonded to aminopropyl-silica gel (5 μm particle size, spherical, pore size 60 Å; 4.6 mm internal diameter, 25 cm in length).

Flow agent: hexane/ethanol = 100/5.

Flow rate: 0.75 ml/minute.

Temperature: 22° C.

The fractions eluted at 31.2 minutes and at 32.9 minutes (UV detection at 254 nm) were separately recovered, collected and evaporated in vacuo.

The following was obtained from the 31.2-minute eluate:

7.5 mg of ethyl (±)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

M.p. 117°-119° C.

Specific rotation: $[\alpha]_D^{20} = +7.0°$ (c = 1.03 in methanol).

The following was obtained from the 32.9-minute eluate:

9.4 mg of ethyl (−)-2-ethoxy-4-N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate.

m.p. 115°-117° C.

Specific rotation: $[\alpha]_D^{20} = -6.9°$ (c = 1.02 in methanol).

Analogous to Example 22,

(a) Ethyl (±)-2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

was separated into its (+) enantiomer and its (−) enantiomer.

EXAMPLE 23

Ethyl
2-acetoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzoate

A mixture of 0.20 g (0.46 mmol) of ethyl 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonyl-methyl]-benzoate, 0.34 ml (3.65 mmols) of acetic acid anhydride and 20 µl of concentrated sulfuric acid was stirred for 40 hours at 70° C. The mixture was then evaporated in vacuo, the residue was taken up in a mixture of water and ether, and neutralized with sodium carbonate. The etheral phase was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic etacts were dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 19/1).

Yield: 50% of theory.

M.p. 133°–135° C. (from petroleum ether).

Calculated: C-69.98%; H-7.55%; N-5.83% Found: C-69.75%; H-7.32%; N-5.74%.

The following compounds were obtained by a procedure analogous so that described in Example 23:

(a) 2-Acetoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-amino-carbonylmethyl]-benzoic acid

Prepared from 2-hydroxy-4-[N-{1-(2-piperidino-phenyl)-butyl}-aminocarbonylmethyl]-benzoic acid.

Yield: 12% of theory.

M.p. 125°–127° C.

Calculated: Mol peak m/e = 452. Found: Mol peak m/e = 452.

(b) Ethyl 2-acetoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared from ethyl 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Yield: 23.5% of theory.

M.p. 163°–166° C.

Calculated: C-72.35%; H-6.66%; N-5.44%.

Found: C-72.41%; H-6.75%; N-5.31%.

(c) 2-Acetoxy-4-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid

Prepared from 2-hydroxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid.

Yield: 17% of theory.

M.p. 126°–128° C.

Calculated: C-71.58%; H-6.21%; N-5.76%. Found: C-71.77%; H-6.57%; N-5.81%.

EXAMPLE 24

2-
Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonyl-methyl]-toluene

A mixture of 0.54 g (1.2 mmols) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzyl chloride (melting point 114°–115° C., prepared from 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl-benzyl alcohol and thionyl chloride in chloroform) and 10 ml of absolute dioxane was hydrogenated for 3 hours at 20° C. and a pressure of 5 bar hydrogen. The reaction mixture was then evaporated in vacuo, and the residue was taken up in a mixture of ethyl acetate and aqueous sodium carbonate. The organic phase was dried, filtered and evaporated in vacuo. The evaporation residue was purified by column chromatography on silica gel (chloroform-/acetone = 19/1).

Yield: 0.23 g (47% of theory).

M.p. 107°–108° C.

Calculated: C-76.43%; H-8.88%; N-6.86%. Found: C-76.40%; H-8.88%; N-6.90%.

EXAMPLE 25

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonyl-methyl]-benzoic acid

100 mg (0.20 mmol) of tert.butyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonyl]-benzoate were refluxed in 5 ml of benzene together with a few crystals of p-toluene-sulfonic acid hydrate for half a day. The desired product was obtained, as confirmed by thin-layer chromatography, by the R_f-value and mass spectrum.

M.p. 87°–89° C.

Calculated: m/e = 438. Found: m/e = 438.

EXAMPLE 26

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonyl-methyl]-benzoic acid

0.25 g (0.47 mmol) of benzyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoate was hydrogenated in 10 ml of ethanol with 0.12 g of 10% palladium-on-charcoal at 50 and a pressure of 5 bar of hydrogen. After 5 hours the catalyst was filtered off through diatomaceous earth, and the filtrate was evaporated in vacuo. The evaporation residue was crystallized from petroleum ether/ethanol.

Yield: 01.4 g (70% of theory).

M.p. 87°–90° C.

Calculated: C-71.21%; H-7.81%; N-6.39%. Found: C-71.46%; H-7.95%; N-6.51%.

EXAMPLE 27

Ethyl
2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-n-hexyl}-aminocarbonylmethyl]-benzoate

Prepared from 1-(2-piperidino-phenyl)-1-n-hexylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid analogous to Example 1.

Yield: 43% of theory.

M.p. 101°–105° C.

Calculated: C-72.84%; H-8.56%; N-5.66%. Found: C-72.72%; H-8.52%; N-5.63%.

EXAMPLE 28

2-Ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-n-hexyl}-aminocarbonyl-methyl]-benzoic acid

Prepared from ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-n-hexyl}-aminocarbonylmethyl]-benzoate analogous to Example 4.

Yield: 77% of theory.

M.p. 117°–120° C.

Calculated: C-72.07%; H-8.21%; N-6.00%. Found: C-72.00%; H-8.06%; N-5.90%.

EXAMPLE 29

[2-Ethoxy-4-[N-(1(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-phenyl]-acetonitrile

To a solution of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl chloride (2 g; 4.5 mmol) [prepared from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)1-butyl)-aminocarbonylmethyl]-ben-

zyl alcohol with thionyl chloride in chloroform], is added sodium cyanide (0.255 g, 5.2 mmol), dissolved in water (2.2 ml), and the phase transfer catalyst benzyl tributylammonium chloride (0.069 g, 0.22 mmol) and the mixture is stirred for 5 days at ambient temperature. Then, further phase transfer catalyst (0.069 g) is added, together with a few small grains of potassium iodide and sodium cyanide (0.2 g) in water (1 ml) and the mixture is stirred for a further 24 hours; then the same amounts of these three components are added again and the mixture is stirred for a further 12 hours. Methylene chloride (40 ml) is added and the mixture is extracted twice with water. The methylene chloride phase is dried over sodium sulphate/potassium carbonate, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).

Yield: 1.53 g.

Melting point: 116°–118° C. (methylene chloride/ether)

Calculated: C 74.79; H 8.14; N 9.69. Found: C 74.86; H 8.19; N 9.42.

EXAMPLE 30

[2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetonitrile

A solution of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzyl chloride (2.6 g, 5.45 mmol) in dimethylsulphoxide (10 ml) is added dropwise at 50°–60° C. to sodium cyanide (0.32 g, 6.5 mmol) in dimethylsulphoxide (40 ml). The mixture is then stirred for 5 hours at 60° C., added to water and extracted with chloroform. The extract is concentrated by evaporation in vacuo. The residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).

Yield: 1.2 g.

Melting point: 145°–148° C.

Calculated: C 77.05; H 7.11; N 8.99. Found: C 76.92; H 7.05; N 8.78.

EXAMPLE 31

Ethyl
[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-acetate

Dry hydrogen chloride is introduced for 3 hours into a stirred and boiling solution of [2-ethoxy-4-[N-(1)2-piperidino-phenyl)-1-butyl)-aminocarbonymethyl]-phenyl]-acetonitrile (1.3 g, 3 mmol) in absolute ethanol (30 ml). The mixture is then evaporated down in vacuo, water (25 ml) is added to the evaporation residue and this is stirred for 15 minutes at 50° C. The mixture is adjusted to a pH of 7 by the addition of solid sodium hydrogen carbonate and is extracted three times with ethyl acetate. The combined organic extracts are shaken once with water, then dried over sodium sulphate/potassium carbonate, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate = 9/1).

Yield: 1.0 g.

Melting point: 91°–93° C. (petroleum ether)

Calculated: C 72.47; H 8.39; N 5.83. Found: C 72.73; H 8.68; N 5.71.

EXAMPLE 32

Methyl
[2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetate

Dry hydrogen chloride is introduced for 4 hours into a stirred and refluxed solution of [2-ethoxy-4-(N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetonitrile (1.2 g, 2.57 mmol) in methanol (20 ml). The mixture is then concentrated by evaporation, added to water and extracted with chloroform. The extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 4/1).

Yield: 340 mg.

Melting point: 136°–138° C. (acetonitrile/water).

Calculated: molecular peak m/e = 500. Found: molecular peak m/e = 500.

EXAMPLE 33

[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl-amino-carbonylmethyl]-phenyl]-acetic acid

A 1N sodium hydroxide solution (2.8 ml) is added to ethyl [2-ethoxy-4-[N-(1-(2-piperidino-phenyl)- 1-butyl-aminocarbonylmethyl]-phenyl]-acetate (0.67 g, 1.4 mmol) in ethanol (10 ml) and stirred for 4 hours at ambient temperature. Then the mixture is evaporated down in vacuo at 50° C. Water and a few drops of methanol are added to the evaporation residue which is then adjusted to pH 6 with 1N acetic acid. It is cooled in ice, whereupon a precipitate is formed This is filtered off and recrystallised from ethanol.

Yield: 0.47 g.

Melting point: 158°–159° C. (ethanol)

Calculated: C 71.65; H 8.02; N 6.19. Found: 71.35; H 8.30; N 6.21.

EXAMPLE 34

[2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetic acid

Prepared analogously to Example 33 by alkaline saponification of methyl [2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-acetate

Melting point: 146°–148° C.

Calculated: C 74.05; H 7.04; N 5.76. Found: C 73.70; H 7.00; N 5.85.

EXAMPLE 35

Ethyl
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamate

A solution of ethyl diethyl-phosphono-acetate (1.68 g, 7.5 mmol) in absolute dioxan (3 ml) is slowly added dropwise, with vigorous stirring, to a suspension of 55% sodium hydride (in oil) (0.327 g, 7.5 mmol) in absolute dioxan (4 ml). After the reaction has died down the mixture is heated to 80° C. for a further 45 minutes. It is then cooled to ambient temperature, a solution of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl-methyl]-benzaldehyde (2.11 g, 5 mmol) [prepared form the corresponding benzyl alcohol by oxidation with pyridinium chlorochromate in chloroform] in absolute dioxan (4 ml) is added dropwise thereto and the mixture is heated for 2 hours at 50° C.

The reaction mixture is pured onto ice/water and extracted with chloroform. The organic extract is dried and filtered and evaporated down in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate = 19/1).

Yield: 1.64 g,

Melting point: 130°-131° C. (ether)

Calculated: C 73.14; H 8.18; N 5.69. Found: C 73.36; H 8.34; N 5.75.

EXAMPLE 36

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-cinnamic acid nitrile

Prepared analogously to Example 35 from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-benzaldehyde with diethylphosphono-acetonitrile.

Melting point: 125°-128° C. (petroleum ether)

Calculated: C 75.47; H 7.92; N 9.43. Found: C 75.40; H 7.95; N 9.24.

EXAMPLE 37

Ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-cinnamate

Under a nitrogen atmosphere, 50% sodium hydride (0.19 g, 8mmol) is added to a stirred solution of ethyl diethylphosphono-acetate (1.8 g, 8 mmol) in absolute 1,2-dimethoxy-ethane (10 ml). Then a solution of 2-ethoxy-4-[N-(α-phenyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzaldehyde (2 g, 4.4 mmol) in absolute 1;2-dimethoxy-ethane (15 ml) is added and the mixture is stirred for 30 minutes at ambient temperature. It is concentrated by evaporation in vacuo and the evaporation residue is distributed between water and chloroform. The chloroform extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).

Yield: 0.37 g.

Melting point: 111°-113° C. (cyclohexane).

Calculated: C 75.26; H 7.27; N 5.32. Found: C 75.14; H 7.32; N 5.25.

EXAMPLE 38

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-cinnamic acid

A solution of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl-methyl]-cinnamate (0.49 g, 1 mmol) in ethanol (10 ml) is stirred together with 1N sodium hydroxide solution (2 ml) for 3 days at ambient temperature. The mixture is then concentrated by evaporation in vacuo, water and a few drops of methanol are added to the evaporation residue and this is then adjusted to pH 6 with 1N acetic acid. The precipitate is filtered off, dried and recrystallised from ethyl acetate.

Yield: 0.37 g.

Melting point: 175°-177° C. (decomp.).

Calculated: C 72.39; H 7.81; N 6.03. Found: 72.50; 7.88; 6.06.

EXAMPLE 39

2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-cinnamic acid

Ethyl 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamate (330 mg, 0.62 mmol) is dissolved in ethanol (10 ml) and, after the addition of 4N sodium hydroxide solution (4 ml), stirred for 3 hours at 50° C. Then the mixture is neutralized with 4N hydrochloric acid (4 ml), diluted with water and filtered off from the precipitate. It is then recrystallized from aqueous ethanol.

Yield: 210 mg.

Melting point: 181° C.

Calculated: C 74.67; H 6.87; N 5.62. Found: C 74.72; H 6.76; N 5.42.

EXAMPLE 40

Ethyl 3-[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionate

A solution of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamate (0.54 g, 1.1 mmol) in ethanol (15 ml) is hydrogenated for 1 hour at ambient temperature and under 3 bars of hydrogen on 10% palladium/charcoal (0.1 g). The mixture is filtered, concentrated by evaporation in vacuo and the evaporation residue is crystallized from petroleum ether.

Yield: 0.30 g.

Melting point: 71°-73° C.

Calculated: C 72.84; H 8.56; N 5.66. Found: C 73.19; H 8.54; N 5.70.

EXAMPLE 41

Ethyl 3-[2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionate

Prepared analogously to Example 40 by catalytic hydrogenation of ethyl 2-ethoxy-4-[N-(αphenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamate and subsequent purification by column chromatography on silica gel (cyclohexane/ethyl acetate/methanol = 6/1/0.5).

Melting point: 130° C. (ethanol/water).

Calculated: C 74.97; H 7.63; N 5.30. Found: C 74.65; H 7.61; N 5.15.

EXAMPLE 42

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionic acid

Prepared analogously to Example 40 by catalytic hydrogenation of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid.

Melting point: 112°-114° C.

Calculated: C 72.07; H 8.21; N 6.00. Found: C 72.30; H 8.21; N 6.00.

EXAMPLE 43

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionitrile

Prepared analogously to Example 40 by catalytic hydrogenation of 2-ethoxy-4[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid nitrile.

Melting point: 102°-103° C. (petroleum ether). Calculated: molecular peak m/e = 447. Found: molecular peak m/e = 447.

EXAMPLE 44

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionic acid

Prepared analogously to Example 33 by alkaline saponification of ethyl 3-[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionate and subsequent purification by column chromatography (chloroform/methanol = 9/1).

Melting point: 112°-115° C. (petroleum ether)

Calculated: C 72.07; H 8.21; N 6.00. Found: C 72.40; H 8.21; N 6.03.

EXAMPLE 45

3-[2-Ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid

Prepared analogously to Example 33 by alkaline saponification of ethyl 3-[2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-propionate.

Melting point: 74° C.

Calculated: C 74.37; H 7.25; N 5.60. Found: C 74.29; H 7.31; N 5.27.

EXAMPLE 46

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionitrile

At ambient temperature, p-toluenesulphonic acid chloride (45.8 mg, 0.24 mmol) is added to a mixture of 3-[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionic acid amide, (56 mg, 0.12 mmol) melting point 153°-155° C. [prepared from the corresponding propionic acid by reacting with carbonyldiimidazole and then with ammonia in tetrahydrofuran] and absolute pyridine (0.044 ml). The mixture is stirred for 45 minutes at 20° C. and for 2 hours at 50° to 60° C. After cooling, water is added, the mixture is made alkaline with concentrated ammonia and extracted three times with chloroform. The combined chloroform extracts are washed with water, dried over sodium sulphate, filtered and concentrated evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform-/ethyl acetate = 9/1).

Yield: 11 mg.

Calculated: molecular peak m/e = 447. Found: molecular peak m/e = 447.

EXAMPLE 47

Ethyl 2-ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

To a solution of α-cyclohexylmethyl-2-piperidinobenzylamine (1.13 g, 3.96 mmol) in acetonitrile (11 ml) are added, successively, 3-ethoxy-4-ethoxycarbonyl-phenyl acetic acid (1 g, 3.96 mmol), of triphenylphosphine (1.25 g, 4.76 mmol), triethylamine (1.11 ml, 7.92 mmol) and carbon tetrachloride (0.38 ml, 3.96 mmol) and the mixture is stirred for 15 hours at ambient temperature. It is then concentrated by evaporation in vacuo and partitioned between ethyl acetate and water. The organic extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 10/1).

Yield: 1.4 g.

Melting point: 95°-97° C. (petroleum ether/cyclohexane = 1/1).

Calculated: C 73.81; H 8.52; N 5.38. Found: C 73.98; H 8.49; N 5.61.

EXAMPLE 48

Ethyl 2-ethoxy-4-[N-(α-benzyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from α-benzyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 102°-105° C. (petroleum ether).

Calculated: C 74.68; H 7.44; N 5.44. Found: C 74.73; H 7.68; 5.39.

EXAMPLE 49

2-Ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid

Ethyl 2-ethoxy-4-[N-(α-cyclohexyl-methyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (1.15 g, 2.21 mmol) in ethanol (12 ml) are stirred together with 1N sodium hydroxide solution (3.3 ml) for 2 hours at 50° C. Then 1N hydrochloric acid (3.3 ml) is added and the mixture is cooled in ice. The precipitate formed is filtered off, washed with a little ice cold ethanol and dried in vacuo at 100° C.

Yield: 0.9 g.

Melting point: 153°-156° C. Calculated: C 73.14; H 8.18; N 5.69. Found: C 73.30; H 8.17; N 5.66.

EXAMPLE 50

2-Ethoxy-4-[N-(α-benzyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-benzyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 100°-105° C.

Calculated: C 74.05; H 7.04; N 5.76. Found: C 73.77; 7.10; N 5.50.

EXAMPLE 51

Ethyl 2-ethoxy-4-[N-(α-ethoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

To a mixture of (2-piperidino-phenyl)-glycine-ethyl ester-dihydrochloride (2 g, 5.96 mmol) in acetonitrile (12 ml) are added successively 3-ethoxy-4-ethoxycarbonyl-phenyl-acetic acid, (1.52 g, 6.75 mmol), triethylamine (2.45 ml, 17.9 mmol) and carbon tetrachloride (0.57 ml, 5.96 mmol) and the mixture is stirred overnight at ambient temperature. It is then concentrated by evaporation in vacuo and partitioned between chloroform and water. The organic extract is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 4/1).

Yield: 1.2 g.

Melting point: 100°-103° C. (ether).

Calculated: C 67.72; H 7.31; N 5.64. Found: C 67.87; H 7.46; N 5.61.

EXAMPLE 52

Benzyl
2-ethoxy-4-[N-(α-ethoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 51 from (2-piperidinophenyl)-glycine-ethyl ester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenyl acetic acid.

Melting point: 90°–93° C.

Calculated: molecular peak m/e = 558.

EXAMPLE 53

Benzyl
2-ethoxy-4-[N-(α-methoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 51 from (2-piperidinophenyl)-glycine-methyl ester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenyl acetic acid.

Melting point: 100°–102° C. (ether)

Calculated: C 70.57; H 6.66; N 5.14. Found: C 70.46; H 6.67; N 5.14.

EXAMPLE 54

Benzyl
2-ethoxy-4-[N-(α-propoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 51 from (2-piperidinophenyl)-glycine-n-propylester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenylacetic acid.

Melting point: 100°–102° C. (petroleum ether)

Calculated: C 71.31; H 7.04; N 4.89. Found: C 71.62; H 7.01; N 4.97.

EXAMPLE 55

Benzyl
2-ethoxy-4-[N-(α-isopropoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 51 from (2-piperidinophenyl)-glycine-isopropylester-dihydrochloride and 3-ethoxy-4-benzyloxycarbonyl-phenylacetic acid.

Melting point: 85°–88° C. (acetone/petroleum ether)

Calculated: C 71.31; H 7.04; N 4.89. Found: C 71.64; H 7.10; N 4.77.

EXAMPLE 56

Ethyl
4-[N-(α-ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoate

Prepared analogously to Example 51 from (2-piperidinophenyl)-glycine-ethylester-dihydrochloride and 4-ethoxycarbonyl-3-hydroxy-phenylacetic acid.

Melting point: 107°–110° C. (petroleum ether)

Calculated: C 66.65; H 6.88; N 5.98. Found: C 66.60; H 6.86; N 6.03.

EXAMPLE 57

Ethyl
2-ethoxy-4-[N-[N-(α-hydroxymethyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

First, 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid (2.52 g, 10 mmol) and N,N'-carbonyldiimidazole (1.62 g, 10 mmol) are heated to 70° C. for 45 minutes in absolute tetrahydrofuran (15 ml). A solution of 2-hydroxy-1-(2-piperidino-phenyl)-1-ethylamine (2.07 g, 9.4 mmol) [prepared by reducing (2-piperidino-phenyl)-glycine-ethylester with lithium aluminium hydride in ether] in absolute tetrahydrofuran (7 ml) is added thereto and the mixture is refluxed for 1 hour. After standing overnight it is diluted with ethyl acetate (50 ml) and shaken twice with water (30 ml). The organic phase is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/methanol = 19/1).

Yield: 2.4 g.

Melting point: 127°–128° C. (acetone)

Calculated: C 68.70; H 7.54; N 6.16. Found: C 68.80; H 7.58; N 6.15.

EXAMPLE 58

Benzyl
2-ethoxy-4-[N-(α-hydroxymethyl-2-piperidinobenyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 57 from 3-ethoxy-4-benzyloxycarbonyl-phenylacetic acid and 2-hydroxy-1-(2-piperidino-phenyl)-1-ethylamine.

Melting point: 89°–91° C. (acetone/ether)

Calculated: C 72.07; H 7.02; N 5.42. Found: C 72.10; H 7.15; N 5.29.

EXAMPLE 59

2-Ethoxy-4-[N-(α-carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Ethyl 2-ethoxy-4-[N-(α-ethoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate (0.45 g, 0.9 mmol) in ethanol (5 ml) is stirred together with 1N sodium hydroxide solution (2.7 ml) for 2 hours at 50° C. Then 1N hydrochloric acid (2.7 ml) is added and the mixture is concentrated by evaporation in vacuo. The evaporation residue is partitioned between water and chloroform. The combined chloroform extracts are shaken once with water, then the organic phase is dried, filtered and evaporated down in vacuo. The evaporation residue is crystallized with ether.

Yield: 0.27 g.

Melting point: 222°–225° C. (decomp.).

Calculated: C 65.44; H 6.41; N 6.36. Found: C 65.58; H 6.59; N 6.28.

EXAMPLE 60

4-[N-(α-Carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoic acid

Prepared analogously to Example 59 by alkaline saponification of ethyl 4-[N-(α-ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxybenzoate.

Melting point: 220°–228° C.

Calculated: C 64.07; H 5.87; N 6.79. Found: C 63.84; H 5.95; N 7.13.

EXAMPLE 61

2-Ethoxy-4-[N-(α-hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 59 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate and purification by column chromatography on silica gel (chloroform/ethanol = 95/5).

Melting point: 80°–81° C. (decomp., sintering from 75° C.)

Calculated: molecular peak m/e=426. Found: molecular peak m/e=426.

EXAMPLE 62

Ethyl
2-ethoxy-4-[N-(α-carboxy-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Ethyl 2-ethoxy-4-[N-(α-ethoxycarbonyl-2-piperidinobenzyl)aminocarbonylmethyl]-benzoate (0.45 g, 0.9 mmol) in ethanol (5 ml) is stirred together with 1N sodium hydroxide solution (0.90 ml) for 4 hours at ambient temperature. Then 1N hydrochloric acid (0.90 ml) is added and the mixture is evaporated down in vacuo. The residue is partitioned between water and chloroform, the chloroform solution is dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethanol=5/1).

Yield: 0.23 g.

Melting point: 177°-180° C. (ether).

Calculated: C 66.65; H 6.88; N 5.98. Found: C 66.65; H 7.11; N 5.79.

EXAMPLE 63

Ethyl
4-[N-(α-carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoate

Prepared analogously to Example 62 by alkaline saponification of ethyl 4-[N-(α-ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxybenzoate.

Melting point: 156°-159° C. (ether).

Calculated: C 65.44; H 6.41; N 6.36. Found: C 65.66; H 6.38; N 6.33.

EXAMPLE 64

Benzyl
2-ethoxy-4-[N-(α-carboxy-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 62 by alkaline saponification of benzyl 2-ethoxy-4-[N-(α-methoxycarbonyl-2-piperidino-benzyl)-aminocarbonyl methyl]-benzoate in dioxan.

Melting point: 140°-142° C.

Calculated: C 70.17; H 6.46; N 5.28. Found: C 70.21; H 6.50; N 5.31.

EXAMPLE 65

Ethyl
2-ethoxy-4-[N-(α-acetoxymethyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

To a solution of ethyl 2-ethoxy-4-[N-(α-hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (0.227 g, 0.5 mmol) and absolute triethylamine (0.126 ml, 0.9 mmol) in absolute chloroform (3 ml), a solution of acetyl chloride (0.063 ml, 0.9 mmol) in absolute chloroform (1 ml) is added dropwise. After 4 days' stirring at ambient temperature the mixture is diluted with chloroform, washed with dilute aqueous sodium bicarbonate solution, the chloroform solution is dried and filtered and evaporated down in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/acetone=4/1).

Yield: 0.17 g.

Melting point: 107°-109° C. (ether/petroleum ether)

Calculated: C 67.72; H 7.31; N 5.64. Found: C 67.70; H 7.48; N 5.74.

EXAMPLE 66

Benzyl
2-ethoxy-4-[N-(α-acetoxymethyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 65 from benzyl 2-ethoxy-4-[N-(α-hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate with acetyl chloride.

Calculated: molecular peak m/e=558. Found: molecular peak m/e=558.

EXAMPLE 67

Benzyl
2-ethoxy-4-[N-(α-propionyloxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Examine 65 from benzyl 2-ethoxy-4-[N-(60-hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate with propionyl chloride.

Melting point: 73°-74° C.

Calculated: C 71.31; H 7.04; N 4.89. Found: C 71.20; H 7.10; N 4.61.

EXAMPLE 68

2-Ethoxy-4-]N-(α-ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

A solution of benzyl 2-ethoxy-4-[N-(α-ethoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (0.140 g, 0.25 mmol) in ethanol (1.4 ml) is hydrogenated with 10% palladium/charcoal (0.03 g) for 4.5 hours at 50° C. under 5 bar of hydrogen. The mixture is filtered, evaporated down in vacuo and the evaporation residue is purified by column chromatography on silica gel (chloroform/methanol=10/1).

Yield: 0.041 g.

Melting point: 115°-118° C. (petroleum ether).

Calculated: molecular peak m/e=468. Found: molecular peak m/e=468.

EXAMPLE 69

2-Ethoxy-4-[N-(α-methoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Examine 68 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-(α-methoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in methanol.

Melting point: 147°-150° C. (decomp.) (ether)

Calculated: C 66.06; H 6.65; N 6.16. Found: C 66.28; H 6.56; N 5.90.

EXAMPLE 70

2-Ethoxy-4-[N-(α-n-propoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 68 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-(α-n-propoxycarbonyl-2-piperidino-benzyl)-aminocarbonyl methyl]-benzoate in n-propanol.

Melting point: 122°-125° C. (ether/petroleum ether=1/1).

Calculated: C 67.20; H 7.10; H 5.80. Found: C 67.39; H 7.24; H 5.78.

EXAMPLE 71

2-Ethoxy-4-[N-(α-isopropoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 68 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-(α-isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in isopropanol.

Melting point: 149°-151° C. (acetone/petroleum ether)

Calculated: C 67.20; H 7.10; N 5.80. Found: C 67.50; H 6.99; N 5.78.

EXAMPLE 72

2-Ethoxy-4-[N-(α-acetoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 68 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-(α-acetoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in ethanol.

Calculated: molecular peak m/e=468. Found: molecular peak m/e=468.

EXAMPLE 73

2-Ethoxy-4-[N-(α-propionyloxymethyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 68 by catalytic hydrogenation of benzyl 2-ethoxy-4-[N-(α-propionyloxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in ethanol.

Melting point: 64°-67° C. (ethanol/water).

Calculated: molecular peak m/e=482. Found: molecular peak m/e=482.

EXAMPLE 74

2-Hydroxy-4-[N-(α-isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Boron tribromide (0.04 ml, 0.414 mmol) is added at −20° C. with the exclusion of moisture to a stirred solution of 2-ethoxy-4-[N-(α-isopropoxycarbonyl-2-piperidino-benzyl)-amino-carbonylmethyl]-benzoic acid (0.20 g, 0.414 mmol) in 1,2-dichloroethane (5 ml). The mixture is allowed to come up to ambient temperature and is then stirred for 2 hours. It is poured into isopropanol, the mixture is concentrated by evaporation in vacuo, water is added and the mixture is extracted with chloroform. The organic extract is dried and filtered and evaporated down in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform methanol/glacial acetic acid=5/1/0.01).

Yield: 0.14 g.

Melting point: 190°-200° C. (ether).

Calculated: molecular peak m/e=454. Found: molecular peak m/e=454.

EXAMPLE 75

Ethyl 2-ethoxy-4-[N-(α-ethoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Ethyl 2-ethyl-4-[N-(α-hydroxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (0.64 g, 1.4 mmol) is added with stirring at ambient temperature to sodium hydride (0.061 g, 1.4 mmol) (55% in oil) in absolute tetrahydrofuran (6.4 ml). The mixture is stirred for 1 hour, then ethyl iodide (0.113 ml, 1.4 mmol) is added and the mixture is stirred for a further 16 hours at ambient temperature. Then ethanol (2 ml) is added and the mixture is evaporated down in vacuo. The evaporation residue is partitioned between chloroform and water. The organic phase is washed twice with water, dried, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform-/acetone=17/3).

Yield: 0.05 g.

Melting point: 85°-87° C. (petroleum ether).

Calculated: molecular peak m/e=482. Found: molecular peak m/e=482.

EXAMPLE 76

2-Ethoxy-4-[N-(α-ethoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 31 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-ethoxymethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Calculated: molecular peak m/e=454. Found: molecular peak m/e=454.

EXAMPLE 77

4-[N-(α-Carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-2-hydroxy-benzoic acid

Prepared analogously to Example 74 by reacting 2-ethoxy-4-[N-(α-isopropoxycarbonyl-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid with 2.5 equivalents of boron tribromide in methylene chloride.

Melting point: 220°-230° C. (water).

Calculated: C 64.07; H 5.87; N 6.79. Found: C 64.21; H 5.99; N 6.81.

EXAMPLE 78

3-[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionitrile

Magnesium chips (0.11 g, 4.5 mmol) are added to 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid nitrile (0.05 g, 0.11 mmol) in methanol (1.1 ml) and the mixture is stirred for 45 minutes at 25° C. and for 1 hour at 0° C. It is then cooled to 0° C. and mixed with of 1N hydrochloric acid (4.5 ml). It is diluted with water, filtered over kieselguhr and extracted with chloroform. The chloroform extract is washed with aqueous sodium bicarbonate solution, dried and filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethyl acetate=9/1).

Yield: 0.015 g.

Melting point: 102°-104° C. (petroleum ether).

Calculated: molecular peak m/e=447. Found: molecular peak m/e=447.

EXAMPLE 79

[2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-phenyl]-acetonitrile

Prepared analogously to Example 29 from 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzyl chloride with sodium cyanide.

Melting point: 135°-136° C.

Calculated: C 75.13; H 8.33; N 9.39. Found: C 75.12; H 8.18; N 9.18.

EXAMPLE 80

Ethyl
2-ethoxy-4-[N-(α-cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from α-cyclopropylmethyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 126°-127° C.

Calculated: C 72.77; H 8.00; N 5.85. Found: C 72.85; H 7.74; N 5.84.

EXAMPLE 81

2-Ethoxy-4-[N-(α-cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid hemihydrate

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 103°-104° C.

Calc. (x 0.5 H_2O): C 70.55; H 7.68; N 6.10. Found: C 70.67; H 7.67; N 6.37.

EXAMPLE 82

Ethyl
2-ethoxy-4-[N-(α-cyclobutylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from α-cyclobutylmethyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenyl acetic acid.

Melting point: 116°-118° C.

Calculated: C 73.14; H 8.18; N 5.69. Found: C 73.14; H 8.32; N 5.64.

EXAMPLE 83

2-Ethoxy-4-[N-(α-cyclobutylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-cyclobutylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 140°-142° C.

Calculated: C 72.39; H 7.81; N 6.03. Found: C 72.15; H 7.79; N 5.97.

EXAMPLE 84

Ethyl
2-ethoxy-4-[N-(α-cyclopenthylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from α-cyclopenthylmethyl-2-piperidino-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenyl-acetic acid.

Melting point: 120°-121° C.

Calculated: C 73.49; H 8.36; N 5.53. Found: C 73.31; H 8.55; N 5.39.

EXAMPLE 85

2-Ethoxy-4-[N-(α-cyclopenthylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-cyclopenthylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 85°-88° C.

Calculated: C 72.77; H 8.00; N 5.85. Found: C 72.50; H 8.02; N 6.03.

EXAMPLE 86

Ethyl
2-ethoxy-4-[N-(2-piperidino-α-(tetrahydrofuran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from 2-piperidino-α-(tetrahydrofuran-2-yl-methyl)-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 111°-113° C.

Calculated: C 70.84; H 7.93; N 5.51. Found: C 70.76; H 7.73; N 5.51.

EXAMPLE 87

2-Ethoxy-4-[N-(2-piperidino-α-(tetrahydrofuran-2-ylmethyl)-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(2-piperidino-α-(tetrahydrofuran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 121°-123° C.

Calculated: C 69.98; H 7.55; N 5.83. Found: C 69.90; H 7.78; N 5.71.

EXAMPLE 88

Ethyl
2-ethoxy-4-[N-(α-cycloheptylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from α-cycloheptylmethyl-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 96°-98° C.

Calculated: C 74.12; H 8.67; N 5.24. Found: C 74.40; H 8.87; N 5.39.

EXAMPLE 89

2-Ethoxy-4-[N-(α-cycloheptylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-cycloheptylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 127°-130° C.

Calculated: C 73.49; H 8.36; N 5.53. Found: C 73.54; H 8.62; N 5.47.

EXAMPLE 90

Ethyl
2-ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

a) Ethyl 2-ethoxy-4-[N-(α-(cyclohexyl-methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from α-cyclohexylmethyl-(2-piperidino-phenyl)-ketimine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 85°-88° C.

Calculated: C 74.10; H 8.16; N 5.10. Found: C 74.37; H 8.00; N 5.45.

According to the 80 MHz-^{1}H-NMR spectrum ($CDCl_3$) there is a mixture of E/Z = ½. [Olefinic H: (E) D 6.26, (Z) 5.42 ppm].

b) Ethyl 2-ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 40 by catalytic hydrogenation of ethyl 2-ethoxy-4-[N-(α-cyclohexyl-

methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 95°–97° C.

Calculated: C 73.81; H 8.52; N 5.38. Found: C 73.92; H 8.74; N 5.29.

EXAMPLE 91

2-Ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

a) 2-Ethoxy-4-[N-(α-cyclohexyl-methylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(α-(cyclohexylmethylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 95°–100° C.

Calculated: C 73.44; H 7.81; N 5.71. Found: C 73.38; H 7.73; N 5.75.

b) 2-Ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 40 by catalytic hydrogenation of 2-ethoxy-4-[N-(α-cyclohexylmethylidene)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid.

Melting point: 154°–156° C.

Calculated: C 73.14; H 8.18; N 5.69. Found: C 73.31; H 8.25; N 5.71.

EXAMPLE 92

Ethyl
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from 1-(2-piperidino-phenyl)-3-buten-1-yl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 110°–112° C.

Calculated: C 72.39; H 7.81; N 6.03. Found: C 72.10; H 7.66; N 5.94.

EXAMPLE 93

Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)-aminocarbonylmethyl]-benzoate.

Melting point: 92°–95° C.

Calculated: C 71.53; H 7.39; N 6.42. Found: C 71.27; H 7.42; N 6.42.

EXAMPLE 94

Ethyl
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from 3-methyl-1-(2-piperidino-phenyl)-3-buten-1-yl)-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 126°–128° C.

Calculated: C 72.77; H 8.00; N 5.85. Found: C 72.82; H 8.22; N 5.78.

EXAMPLE 95

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]-benzoate.

Melting point: 64°–66° C.

Calculated: C 71.97; H 7.61; N 6.22. Found: C 71.70; H 7.50; N 5.98.

EXAMPLE 96

Ethyl
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-2-buten-1-yl)-aminocarbonylmethyl]-benzoate[with 25% of ethyl
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate]

Prepared analogously to Example 47 from 3-methyl-1-(2-piperidino-phenyl)-2-buten-1-yl-amine [containing 25% of 3-methyl-1-(2-piperidino-phenyl)-1-butylamine] and 3-ethoxy-4-ethoxycarbonylphenylacetic acid.

Melting point: 141°–142° C.

Calculated: C 72.77; H 8.00; N 5.85. Found: C 72.60; H 7.77; N 5.73.

The mixing ratio of 75/25 is obtained from the corresponding ratio of intensities of the particularly characteristics signals in the 400 MHz-^{1}H-NMR spectrum ($CDCl_3$). The position of the signals is: 3-methyl-2-buten-1-yl compound: olefinic H: 5.25 (d), CH_3: 1.64 (s) and 1.77 (s); benzylic >CH— 6.00 (t), benzylic CH_2—; 3.52 ppm (s) 3-methyl-1-butyl compound: CH_3: 0.90 (d), benzylic >CH— 5.35 (m), benzylic —CH_2—; 3.54 ppm (s).

EXAMPLE 97

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-2-buten-1-yl)-aminocarbonylmethyl]-benzoic acid [containing 25% of
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid]

Prepared analogously to Example 49 by alkaline saponification of the corresponding ethyl ester mixture from Example 68.

Melting point: 154°–156° C.

Calculated: C 71.97; H 7.61; N 6.22. Found: C 71.80; H 7.57; N 5.98.

EXAMPLE 98

Ethyl
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyn-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from 1-(2-piperidino-phenyl)-3-butyn-1-yl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 86°–90° C.

Calculated: C 72.70; H 7.41; N 6.06. Found: C 72.60; H 7.40; N 6.04.

EXAMPLE 99

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyn-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 21 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyn-1-yl)-aminocarbonylmethyl]-benzoate.

Melting point: 66°–69° C.

Calculated: C 71.87; H 6.96; N 6.45. Found: C 71.60; H 6.95; N 6.38.

EXAMPLE 100

Ethyl
2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from 1-(2-piperidino-phenyl)-4-penten-1-yl-amine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 117°-120° C.

Calculated: C 72.77; H 8.00; N 5.85. Found: C 72.73; H 7.97; N 6.07.

EXAMPLE 101

2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoate.

Melting point: 82°-85° C.

Calculated: C 71.97; H 7.61; N 6.22. Found: C 71.97; H 7.59; N 5.98.

EXAMPLE 102

Ethyl
2-ethoxy-4-[N-(1-(2-piperidino-α-(tetrahydropyran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 47 from 2-piperidino-α-(tetrahydropyran-2-yl-methyl)-benzylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid.

Melting point: 82°-85° C.

Calculated: C 71.24; H 8.10; N 5.36. Found: C 71.28; H 7.96; N 5.29.

EXAMPLE 103

2-Ethoxy-4-[N-(1-(2-piperidino-α-(tetrahydropyran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoic acid

Prepared analogously to Example 49 by alkaline saponification of ethyl 2-ethoxy-4-[N-(1-(2-piperidino-α-(tetrahydropyran-2-yl-methyl)-benzyl)-aminocarbonylmethyl]-benzoate.

Melting point: 140°-142° C. (sinters from 70° C., partial softening at 105° C.).

Calculated: C 70.42; H 7.74; N 5.66. Found: H 7.88; N 5.40.

Ethyl
2-ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

At 23°-25° C., a solution of 2-ethoxy-4-cyanomethyl-benzoate (2.35 g, 10 mmol) and α-cyclohexylmethyl-2-piperidino-benzyl alcohol (2.88 g, 10 mmol) in o-dichlorobenzene (15 ml) is added dropwise to a mixture of concentrated sulphuric acid (15 ml) and o-dichlorobenzene (15 ml). The mixture is stirred for 2 hours at ambient temperature. The o-dichlorobenzene phase is then separated off and the residue is added to ice. After being made alkaline with soda solution, it is extracted with chloroform. The extracts are dried over sodium sulphate and concentrated by evaporation. The residue is purified by column chromatography on silica gel (toluene/acetone = 10/1).

Yield: 1.1 g.

Melting point: 95°-97° C.

Calculated: C 73.81; H 8.52; N 5.38. Found: C 73.95; H 8.64; N 5.42.

EXAMPLE 105

Benzyl
2-ethoxy-4-[N-(α-methoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Potassium carbonate (0.28 g, 2 mmol) is added to a solution of benzyl 2-ethoxy-4-[N-(α-carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate (1.06 g, 2 mmol) in anhydrous dimethyl formamide (8 ml). The mixture is stirred for 10 minutes at ambient temperature, then methyl iodide (0.125 ml, 2 mmol) is added and the resulting mixture is stirred overnight at ambient temperature. It is filtered and the filtrate is concentrated by evaporation to dryness in vacuo. The evaporation residue is partitioned between aqueous sodium bicarbonate solution (pH = 9) and methylene chloride. The organic phase was poured over sodium sulphate, filtered and concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 4/1) and crystallised from ether/petroleum ether.

Yield: 0.56 g.

Melting point: 100°-102° C.

Calculated: C 70.57; H 6.66; N 5.14. Found: C 70.69; H 6.71; N 5.29.

EXAMPLE 106

(S)
2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoic acid

a) (S)-3-Methyl-1-(2-piperidino-phenyl)-1-butylamine

Equimolar quantities of racemic 3-methyl-1-(2-piperidino-phenyl)-1-butylamine and of N-acetyl-L-glutamic acid were refluxed in aceton, whereby methanol was added in such an amount to yield a clear solution.

After cooling over night up to 20° C., the obtained crystals were suction filtered and twice washed with aceton cooled to −15° C. The obtained product [M.p.: 163°-166° C.; $[\alpha]_D^{20} = +0{,}286°$ (c = 1 in methanol)] was recrystallised from aceton under addition of methanol, whereby (S)-3-methyl-1-(2-piperidino-phenyl)-1-butylamine as N-acetyl-L-glutamic acid addition salt was obtained in a yield of 60,4% of theory.

M.p.: 168°-171° C.

$[\alpha]_{20}^{D} + 0{,}356°$ (c = 1 in methanol).

The free amine was obtained after reacting with sodium hydroxide solution.

b) (S) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoate

Prepared from (S)-3-Methyl-1-(2-piperidino-phenyl)-1-butylamine and 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid analogously to Example 1.

Yield: 77% of theory.

M.p.: 121°-123° C. (petroleum ether/aceton = 7/1).

$[\alpha]_{20}^{D} + 7{,}82°$ (c = 1 in methanol).

c) (S) 2-Ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoic acid

Prepared from (S) Ethyl 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoate by saponification analogously to Example 4.

Yield: 75.9% of theory.

M.p.: 102°-104° C. (petroleum ether/toluene).

$[\alpha]_{20}^{D} + 7{,}80°$ (c = 1,025 in methanol).

The compounds of the present invention, that is, those embraced by formula I above, including forms (A), (B) and (C) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, their enantiomers and their non-toxic, pharmacologically acceptable salts formed with inorganic or organic acids or bases, have useful pharmacodynamic properties. More particularly, they have a favorable effect on the intermediate metabolism and exhibit hypoglycemic activity in warm-blooded animals such as rats.

The hypoglycemic activity of the compounds of the instant invention was ascertained by the standard pharmacological test method described below, and the table which follows shows the results of this test for a few representative species of the genus, where

A=2-methoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl}-aminocarbonylmethyl]-benzoic acid,

B=2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid,

C=2-methoxy-4-[N-(α-phenyl-2-piperidino-benzyl-)aminocarbonylmethyl]-benzoic acid,

D=2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl-)aminocarbonylmethyl]-benzoic acid,

E=(+)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}aminocarbonylmethyl]-benzoic acid,

F=2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-ethyl-}aminocarbonylmethyl]-benzoic acid,

G=Sodium 2-ethoxy-4-[N-{1-(2-pyrrolidino-phenyl)-1-butyl}aminocarbonylmethyl]-benzoate,

H=2-ethoxy-4-[N-{1-(2-hexamethyleneimino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid,

I=2-methoxy-4-(N-{1-(2-piperidino-phenyl)-1-butyl-}aminocarbonylmethyl]-benzoic acid,

K=2-n-propoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}aminocarbonylmethyl]-benzoic acid,

L=2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-pentyl-}aminocarbonylmethyl]-benzoic acid,

M=2-ethoxy-4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoic acid,

N=form (B) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid,

O=[2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-acetonitrile,

P=[2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]acetonitrile,

Q=2-ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

R=2-ethoxy-4-[N-(α-ethoxycarbonyl-2-piperidino-benzyl)aminocarbonylmethyl]-benzoic acid,

S=2-ethoxy-4-[N-(α-methoxycarbonyl-2-piperidino-benzyl)aminocarbonylmethyl]benzoic acid,

T=2-ethoxy-4-[N-(α-isopropoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,

U=2-ethoxy-4-[N-(α-cyclopropylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,

V=2-ethoxy-4-[N-(α-(tetrahydrofuran-2-yl-methyl)-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,

W=2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-buten-1-yl)aminocarbonylmethyl]benzoic acid,

X=2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-3-buten-1-yl)-aminocarbonylmethyl]benzoic acid and

Y=2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-butyn-1-yl)aminocarbonylmethyl]benzoic acid,

TEST FOR HYPOGLYCEMIC ACTIVITY

the hypoglycemic activity of the test compounds was ascertained on female rats of a particular strain weighing from 180–220 g which had been fasted for 24 hours before the start of the test. The test compounds were suspended in 1.5% methyl cellulose immediately before the start of the test and administered by esophageal tube.

Blood samples were taken immediately before the administration of the test compound and 1, 2, 3 and 4 hours afterwards, in each case from the retroorbital Venous plexus. 50 µl of each sample were deproteinated with 0.5 ml of 0.33N perchloric acid and centrifuged. The glucose in the supernatant fluid was measured using the hexokinase method with the aid of an analytical photometer. The statistical evaluation was made using the t-test according to Student with p=0.05 as the limit of significance.

The following tables show the changes in glucose content in percent compared with the control:

TABLE I

	1 mg/kg				0.5 mg/kg			
Compound	1	2	3	4 h	1	2	3	4 h
A	−37	−46	−23	−14				
B	−38	−49	−38	−33	−43	−36	−34	−35
C	−38	−41	−38	−34				
D	−42	−54	−37	−34				
E					−40	−39	−36	−36
F	−44	−44	−40	−30				
G					−40	−33	−30	−17
H					−42	−34	−18	n.s.
I					−42	−39	−37	−30
K					−34	−36	−24	n.s.
L					−42	−45	−38	−39
M	−44	−41	−35	−27				
O	−29	−37	−35	−34				
P	−12	−10	−14	−14				
Q					−22	−47	−45	−45
R	−33	−17	n.s.	n.s.				
S	−42	−35	−28	−18				
T	−36	−21	−18	n.s.				
U					−45	−45	−36	−36
V					−46	−25	−13	−10
W					−42	−39	−28	−35
X					−44	−41	−31	−28
Y					−33	−18	−11	n.s.

n.s. = not statistically significant

TABLE II

	0.1 mg/kg			
Compound	1	2	3	4 h
N	−38	−44	−41	−40

In the tests for hypoglycemic acitivity, no toxic side effects were observed, even at a dosage of 10 mg/kg p.o., with any of these compounds.

The novel compounds are virtually non-toxic; for example, after a single dose of 2,000 mg/kg p.o. (suspension in 1% methyl cellulose) of compounds B and D to 5 male and 5 female mice, only one animal in this group died during the observation period of 14 days.

The toxic effect of a single dose of compound N administered orally (suspended in 1% methyl cellulose) was tested in male and female mice of our own strain weighing from 20–26 g over an observation period of 14 days.

TABLE III

Compound	Approximate acute toxicity	
N	>1000 mg/kg p.o.	(0 out of 6 animals died)

By virtue of their pharmacological properties, the compounds of the present invention are useful for the treatment of diabetes mellitus.

For pharmaceutical purposes the compounds of the present invention are administered to warm-blooded animals perorally or parenterally as active ingredients in customary pharmaceutical compositions, that is, compositions consisting essentially of an inert pharmaceutical carrier and an effective amount of the active ingredient, such as tablets, coated pills, capsules, wafers, powders, solutions, suspensions, emulsions, syrups and the like. An effective amount of the compounds of the present invention is from 0.014 to 0.71 mgm/kg body weight, preferably 0.035 to 0.29 mgm/kg body weight, once or twice daily.

The following examples illustrates a few pharmaceutical compositions comprising a compound of the present invention as an active ingredient and represent the best modes contemplated of using the invention. The parts are parts by weight unless otherwise specified.

EXAMPLE 107

Tablets containing 5 mg of 2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, form (B)

The tablet composition is compounded from the following ingredients:

Active ingredient	(1)	5.0 parts
Corn starch	(2)	62.0 parts
Lactose	(3)	48.0 parts
Polyvinylpyrrolidone	(4)	4.0 parts
Magnesium stearate	(5)	1.0 parts
		120.0 parts

Preparation

Ingredients (1), (2), (3) and (4) are mixed together and moistened with water. The moist mixture is passed through a 1.5 mm mesh screen and dried at about 45° C. The dry granulate is passed through a 1.0 mm mesh screen and mixed with ingredient (5). The finished mixture is compressed into 120 mg-tablets.

EXAMPLE 108

Coated tablets containing 2.5 mg of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]benzoic acid, form (A)

The tablet core composition is compounded from the following ingredients:

Active ingredient	(1)	2.5 parts
Potato starch	(2)	44.0 parts
Lactose	(3)	30.0 parts
Polyvinylpyrrolidone	(4)	3.0 parts
Magnesium stearate	(5)	0.5 parts
		80.0 parts

Preparation

Ingredients (1), (2), (3) and (4) are thoroughly mixed and moistened with water. The moist mass is passed through a 1 mm-mesh screen, dried at about 45° C., and the granulate is then passed through the same screen. After ingredient (5) has been added, convex 80 mg-tablet cores are compressed in a tablet-making machine. The tablet cores thus produced are covered in known manner with a coating consisting essentially of sugar and talc. The finished tablets are polished with wax. Weight of each coated tablet: 120 mg.

EXAMPLE 109

Tablets containing 10 mg of 2-ethoxy-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

The tablet composition is compounded from the following ingredients:

Active ingredient	10.0 parts
Powdered lactose	70.0 parts
Corn starch	31.0 parts
Polyvinylpyrrolidone	8.0 parts
Magnesium stearate	1.0 parts
	120.0 parts

Preparation

The mixture of active ingredient, lactose and corn starch is moistened with a 20% solution of polyvinylpyrrolidone in water. The moist mass is passed through a 1.5 mm mesh screen and dried at 45° C. The dried granulate is passed through a 1 mm mesh screen and is homogeneously mixed with magnesium stearate. The composition is compressed into 120 mg-tablets.

EXAMPLE 110

Coated tablets containing 5 mg of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]benzoic acid

The tablet core composition is compound from the following ingredients:

Active ingredient	5.0 parts
Secondary calcium phosphate	70.0 parts
Corn starch	50.0 parts
Polyvinylpyrrolidone	4.0 parts
Magnesium stearate	1.0 parts
	130.0 parts

Preparation

The mixture of active ingredient, calcium phosphate and corn starch is moistened with a 15% solution of polyvinylpyrrolidone in water. The moist mass is passed through a 1 mm mesh screen, dried at 45° C. and then passed through the same screen. After adding the magnesium stearate, 130 mg-tablet cores are compressed from the mixture.

A coating of sugar and talc is applied in known manner to the cores thus produced. The finished coated tablets are polished with wax.

Weight of coated tablet: 180 mg.

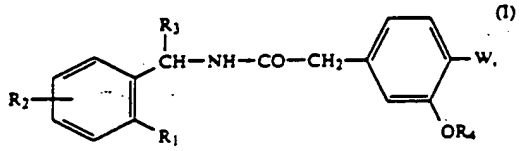
Any one of the other compounds embraced by formula I, including forms (A), (B) and (C) of 2-ethoxy-4-

[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, an enantiomer thereof or a non-toxic, pharmacologically acceptable salt thereof may be substituted for the particular active ingredient in Examples 29 through 32. Likewise, the amount of active ingredient in these illustrative examples may be varied to achieve the dosage unit range set forth above, and the amounts and nature of the inert pharmaceutical carrier ingredients may be varied to meet particular requirements.

While the present invention has been illustrated with the aid of certain specific embodiments thereof, it will be readily apparent to otherwise skilled in the art that the invention is not limited to these particular embodiments, and that various changes and modifications may be made without departing from the spirit of the invention of the scope of the appended claims.

We claim:

1. A compound of the formula:



(I)

wherein

R_1 represents an unbranched alkyleneimino group with 4 to 6 carbon atoms optionally mono- or di-(alkyl of 1 to 3 carbon atoms)-substituted;

R_2 represents a hydrogen or halogen atom or a methyl or methoxy group;

R_3 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by a hydroxy, alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain from 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 or 3 carbon atoms and the cycloalkyl part can contain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms;

R_4 represents a hydrogen atom, a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxyl, alkoxycarbonyl, cyanomethyl, 2-cyano-ethyl, 2-cyano-ethenyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonylethenyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group; and

when R_3 is other then hydrogen and/or the radical R_1 contains an optically active carbon atom, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position.

2. A compound of claim 1, wherein

R_1 represents a pyrrolidino, piperidino, 4-methyl-piperidino, 3-methyl-piperidino, 3,3-dimethyl-piperidino, 3,5-dimethyl-piperidino or hexamethyleneimino group;

R_2 represents a hydrogen, fluorine or chlorine atom;

R_3 represents hydrogen atom, an alkyl group with 1 to 6 carbon atoms, a phenyl, methyl-phenyl, chloro-phenyl, methoxy-phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, tetrahydrofuran-2-yl-methyl, tetrahydropyran-2-yl-methyl, propargyl, hydroxymethyl, ethoxymethyl, acetoxymethyl, propionyloxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl group or an alkenyl group with 3 or 4 carbon atoms;

R_4 represents a methyl, ethyl or allyl group; and

W represents a methyl, hydroxymethyl, formyl, carboxyl, benzyloxycarbonyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, cyanomethyl, 2-carboxy-ethyl, 2-ethoxycarbonyl-ethyl, 2-cyano-ethyl, 2-carboxy-ethenyl, 2-ethoxycarbonyl-ethenyl or 2-cyano-ethenyl group or an alkoxycarbonyl group with 1 to 4 carbon atoms in the alkoxy part; and

when R_3 is other then hydrogen and/or R_1 represents the 3-methyl-piperidino group, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position.

3. A compound of claim 1, wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 1 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, tetrahydropyran-2-yl-methyl, cyclopropylmethyl or cyclohexylmethyl group;

R_4 represents a methyl, ethyl or allyl group; and

W represents a carboxyl, methoxycarbonyl, ethoxycarbonyl or cyanomethyl group; and

the enantiomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

4. A compound of claim 1, wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 3 to 6 carbon atoms, an alkenyl group with 3 or 4 carbon atoms, a phenyl, cyclopropylmethyl or cyclohexylmethyl group;

R_4 represents a methyl or ethyl group; and

W represents a carboxyl group; and

the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

5. A compound of claim 1, wherein

R_1 represents a piperidino group;

R_2 represents a hydrogen atom;

R_3 represents an alkyl group with 3 to 6 carbon atoms, a 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group;

R_4 represents a methyl or ethyl group; and

W represents a carboxyl group; and

the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

6. A compound of claim 5, wherein

R_3 represents a n-propyl, n-butyl, isobutyl, sec.butyl, n-pentyl, 2-methyl-1-propen-1-yl, cyclomethylpropyl or cyclohexylmethyl group;

the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the piperidino function.

7. A compound of claim 5, wherein

R_3 represents a n-propyl, n-butyl, isobutyl, sec.butyl or n-pentyl group; and

the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof salt thereof formed by an inorganic or organic acid with the piperidino function.

8. The compound of claim 5, which is 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid; the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the piperidino function.

9. The compound of claim 5, which is 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]benzoic acid; the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the piperidino function.

10. The compound of claim 5, which is form (A) of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid, recrystallized from acetone/petroleum ether, having a melting point of 90°-92° C.

11. The compound of claim 5, which is form (B) of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid, recrystallized from ethanol/water, having a melting point of 140°-142° C.

12. The compound of claim 5, which is form (C) of 2-ethoxy-4-[N-(1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoic acid, recrystallized from methanol, having a melting point of 74°-85° C.

13. The compound of claim 5, which is 2-ethoxy-4-[N-(α-cyclohexylmethyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid; the enantiomeres thereof or their mixtures; a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the piperidino function.

14. The (S)-enantiomer of a compound as claimed in anyone of the claims 1 to 13; when W is carboxy, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt formed by an inorganic or organic acid with the amino function in the R_1-position.

15. A hypoglycemic pharmaceutical composition consisting essentially of an inert pharmaceutical carrier and an effective hypoglycemic amount of a compound of claim 1.

* * * * *

4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#2

In re:

Application of : W. Grell et al.

Serial No. : 495,820 Group Art Unit : 129

Filed : March 19, 1990 Examiner : B.G. Bembenick

For : PHENYLACETIC ACID BENZYLAMIDES

Commissioner of Patents and Trademarks
Washington, D.C. 20231

TERMINAL DISCLAIMER

Dear Sir:

Dr. Karl Thomae GmbH, a corporation of Germany having a place of business at D-7950 Biberach an der Riss, Germany, represents that it is the exclusive owner of the entire right, title and interest of, in and to application Serial No. 495,820, filed on the 19th day of March, 1990 for PHENYLACETIC ACID BENZYLAMIDES.

It hereby disclaims the terminal part of any patent granted on the above-identified application or any continuation thereof, which would extend beyond the expiration date of Patent No. 4,873,080, issued October 10, 1989, its own prior patent, and hereby agree that any patent so granted on the above-identified application shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to United States Patent No. 4,873,080, this agreement to run with any patent granted on the above-identified application or any continuation thereof, and to be binding upon the grantee, its successors or assigns.

The fee required by 37 C.F.R. 1.20(d) is submitted herewith.

Dr. Karl Thomae GmbH

ppa.
By: _____
Dr. Dieter Laudien
Date: July 23, 1992

ppa.
By: _____
Rodger Milnes
Date: July 23, 1992

Case: 5/891-1-C1

5891.dis

5-891-US

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STA
1	5,216,167	183	1020	----	07/495,820	06/01/93	06/21/90	04	NO	PAI

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	S8911C1

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL-439 (REV. 4-88)

DENNEMEYER & CO
LUXEMBOURG
P.O. Box 1502
L-1015 LUXEMBOURG

01 1700 01

DEBIT NOTE
NOTE DE DEBIT
RECHNUNG

BOEHRINGER INGELHEIM GMBH
A PATENTE

D-55216 INGELHEIM/RHEIN

La	H	Ka	Kl	Kr	Ku
Pl	EINGANG				Ma
Wien	A Patente				Wi
Bib	14. NOV. 1996				Debit Note 2433
	TS:				
					Urk

Page 44

We have paid the undermentioned annuities and debited your account as indicated. Official renewal receipts will be forwarded to you in due course.
Nous avons payé les annuités énumérées et nous avons débité votre compte de la somme indiquée ci-dessous. Les quittances officielles vous parviendront dès réception.
Wir haben die nachstehenden Jahresgebühren eingezahlt und haben Ihr Konto wie folgt belastet. Die amtlichen Quittungen werden wir Ihnen nach Empfang zustellen.

11 NOV 96

Your reference Votre référence Ihr Zeichen	Country Pays Land	Type	Number Numéro Nummer	Tax	Working Licence Ausführung	Due Echéance Fälig	Fee/Montant/Betrag dem
05-0920-US-A	UNITED STATES	PATENT	4843086	08		27 DEC 96	3182.30
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]
05-0948-US-B	UNITED STATES	PATENT	5219852	04		15 DEC 96	1588.40
08-0111-US-C	UNITED STATES	PATENT	5223511	04		29 DEC 96	1588.40
						Page total dem	7947.50

Account:
DEM: KONTO 9811989
DRESDNER BANK, FRANKFURT
BLZ 500 800 00

Accounts:
BEF : 30-241314-12
USD: 30-241314-32-4
NLG: 30-241314-52-8
ATS : 30-241314-47-7
CHF : 30-241314-22-2
FRF : 30-241314-37-5
GBP : 30-241314-27-3
JPY : 30-241314-42-6
Banque Générale, Luxembourg
27, avenue Monterey, Luxembourg

TELEPHONE: 49 98 41-1
TELEX: 2769 DENPAT LU
TELEGRAMME: DENPAT
TELECOPIEUR Gr. III et II: 49 98 41-220

Total paid on your behalf
Commission on items
VAT at
GRAND TOTAL

5

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
2 Mar 92	0.00	Original IND. Provides for an oral hypoglycemic tablet for treatment of Type II diabetes.
6 Mar 92	Form 3228a	FDA acknowledged receipt of IND dated 3/2/92 and assigned IND #39,012.
1 Apr 92	001	Information Amendment: Toxicology re: AG-EE 623 caused developmental limb reduction characterized by growth delay and deformation; observed at interim evaluation point of Segment I & III reproduction toxicology studies. Determined that this effect was probably a post-natal rather than a teratogenic effect.
9 Apr 92	002	Protocol Amendment: revises the investigators' brochure & protocol for study USA/OHA/059/AG as a follow-up to #001 (4/1/92) submission.
14 Apr 92	003	Information Amendment: Toxicology Follow-up to 4/13/92 telephone call to L. Braithwaite, CSO, x-ref to amendments #001 & #002 (4/1 & 4/9/92 respectively). Statement from Chief toxicologist for study concluding that the developmental limb reduction is a pre- & post-natal effect. Will withhold dosing in next study until authorized to do so by FDA.
24 Apr 92	phone	L. Braithwaite, CSO, to S. Rais. FDA will allow the start-up of clinical trials with the oral agent with the stipulation that women of child-bearing potential are not enrolled in the study.
18 Aug 92	Letter	FDA comments to #001 & requests for additional information be submitted in three areas: Medical, Manufacturing/Quality Control and Pharmacology. Also stated study could continue.
7 Mar 93	phone	F. Longenecker to J. Short, CSO to request informal meeting with pharmacologist re: preclinical findings & use of women of child bearing potential in clinical studies. J. Short said to contact pharmacologist directly. (See memo dated March/April 1993 - FDA Contacts).
5 Apr 93	phone	F. Longenecker to J. Short, CSO. Apprise him that we will be filing Amendment #005, containing follow-up reports to pre-clinical observations we had informed FDA about a year ago. Proposed informal meeting with division toxicologist to discuss proposed toxicology research plan for AG-EE 623. J. Short said to contact Dr. Jordan, directly.
13 Apr 93	004	Protocol amendment: New protocol Phase II USA/OHA/061/AG and Form FDA 1572 for S. R. Mather, M.D.
13 Apr 93	005	Information Amendment: Toxicology to support use of women of child bearing potential in clinical studies & study duration up to 3 months. Additionally, an informational meeting was requested to discuss a proposed research plan to investigate the developmental effect seen with AG-EE 623 ZW.
22 & 26 Apr 93	phone	NNPI to J. Short (CSO). At conclusion of discussion on NDA items, FrL informed J. Short of upcoming informal meeting with FDA toxicologists to discuss research plan for investigating neonatal limb effects seen with AG-EE 623 ZW. Call was followed-up

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
		with a telefax copy of this information.
26 Apr 93	Fax	NNPI confirmatory letter notifying John Short, CSO that informal meeting with toxicologists (Drs. Jordan & Rhee) has been set for 5/6/93. X-ref #005.
6 May 93	Meeting	Informal meeting with Drs. Jordan & Rhee, toxicologists in Metabolism/Endocrine Division to discuss (1) including women of child bearing potential in Phase II studies and (2) research plan for evaluating developmental limb effect seen in reproduction toxicology studies.
10 May 93	Minutes	NNPI minutes of meeting of 5 May.
12 May 93	006	Annual Report for March 6, 1992 through February 28, 1993.
6 Aug 93	007	Information Amendment: Chemistry re: additional CMC documentation for 2 mg tablets & encapsulated tablets for future IND clinical studies, including AGEE/DCD/030/USA.
6 Aug 93	008	Protocol Amendment: New Protocol Phase II Study - AGEE/DCD/030/USA & FDA Form 1572 for J. Janick, M.D.
27 Sep 93	Letter	NNPI request to J. Short, CSO to submit NNAS trade name "NovoNorm" for review by FDA trademark committee.
05 Oct 93	009	Protocol Amendment: New Protocol - New Investigator for Protocol AGEE/DCD/031/USA, "proof of concept study". TC Marbury, MD.
26 Oct 93	Letter	Submission to all Diabetes Care DMFs, INDs and NDAs (which had cross-referenced NNAS plant DMF 3536) to change that cross-reference to new DMF 10480 for NNAS DCD Facilities only.
03 Nov 93	010	Protocol Amendment: Revision to Protocol AGEE/DCD/031/USA (filed in 009) to expand inclusion criteria after 1 week stabilization from FBG 80-140 mg/dl to 80-165 mg/dl.
18 Jan 94	011	Protocol for bioequivalence study on 2 mg tablets and encapsulated tablets.
20 Jan 94	012	Protocol AGEE/DCD/032/USA, "Skip-A-Meal (SAM)" study scheduled to start 1/31/94.
21 Jan 94	013	Information (CMC) amendment providing information on blinded active comparative drug (Diaseta) for study AGEE/DCD/032/USA (as well as future IND studies).
13 Apr 94	014	Responses to FDA questions (August 18, 1992) on original IND submission.
6 May 94	015	Annual Report for time period March 1993 - February 1994.

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
11 May 94	016	Submission of Protocols for clinical trials AGEE/DCD/036/USA (Jerry Herron, MD) and AGEE/DCD/033/USA (Robert G. Brodows, MD). Forms 1572 and CVs for other four 033 investigators to be batched and sent later.
12 May 94	Memo	Follow-up to FDA (J. Short) 9/27/93 request for FDA comment on the acceptability of the trade name "NovoNorm"; FDA denied the request and is sending a letter to this effect.
23 May 94	Letter	Decision from FDA that the trade name "Novo Norm" is unacceptable for this product.
6 Jun 94	017	Protocol amendment to delete the continuation criteria at visit 10 (start of the maintenance period); patients not reaching this target range will continue in the 3-month maintenance phase; submission of Forms 1572 & curricula vitae for 4 additional investigators.
7 Sept 94	018	Information amendment to provide results of additional non-clinical pharmacology and toxicology studies.
9 Sept 94	019	Protocol amendment to provide for new Phase III clinical study AGEE/DCD/049/USA to be conducted at 19 sites in the US Canada.
28 Sept 94	020	Information amendment to provide information on the packaging of clinical supplies for the Phase III program.
25 Oct 94	Memo	FDA (J. Short) telephoned to ask if NNPI was planning to request an end of Phase II meeting. Capt Short was advised that a information was being prepared with a request for an end of Phase II meeting in late November or December. Capt. Short was advised that several preclinical and clinical questions were on the agenda; we were asked to include the questions in our submission package.
26 Oct 94	021	Request for an end of Phase II meeting with FDA in late November or December to discuss NNPI's preclinical program and Phase III clinical plans.
27 Oct 94	022	Protocol amendment for AGEE/DCD/049/USA to provide additional investigators for Phase III clinical study.
2 Nov 94	023	Protocol amendment to provide revised investigator information for study AGEE/DCD/033/USA.
8 Nov 94	024	IND Safety Report for serious adverse event (death) which occurred in study ID #B/OHA/038/AG taking place in Belgium. **(Note to file: the reference on the letter states that the submission is a protocol amendment for a new investigator; error has been noted in files.)**
21 Nov 94	025	Information Amendment: reference to information package and request submitted October 26, 1994 (No. 021). The purpose of this submission is to advise the Agency of recent information about the status of the rodent carcinogenicity testing program.

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
22 Nov 94	026	Protocol Amendment: provides for new investigator (Holvey, Sonneberg) information for study AGEE/DCD/049/USA.
23 Nov 94	027	Confirmation of end of phase II meeting with FDA on 12/20/94. (Reference is made to information package & request submitted 10/26/94 (serial no. 021) and teleconference on 11/22/94.)
23 Nov 94	Letter	Follow-up to telephone request from FDA (J. Short) for nine additional copies of serial numbers 021 and 025 of the subject IND in preparation for the end of phase II meeting scheduled for 12/20/94.
29 Nov 94	Memo	FDA (H. Rhee) telephoned concerning the upcoming end of phase II meeting (12/20/94). He inquired about the mouse and rat carcinogenicity studies and whether or not we had achieved maximum tolerated dose (MTD). Dr. Rhee was advised that MTD had been achieved and would be addressed in the presentation at the end of phase II meeting.
9 Dec 94	028	Submission of revisions to the manufacturing and controls information for the drug substance submitted in the original IND and amended in serial no. 007. The bulk drug substance manufactured according to this amendment will be used in the dosage form for clinical study AGEE/DCD/049/USA (serial no. 019).
16 Dec 94	029	Protocol Amendment: provides for new investigator (Lawrence Leiter), two new subinvestigators (Drs. Guerrero & Miller), and revised investigator (Thomas Blevins) information.
22 Dec 94	Memo	FDA (J. Short) initially phoned to request the full titles of the representatives of Novo Nordisk at the end of phase II meeting held 12/20/94. He also requested a replacement copy of the overhead showing serum glucose values in study OHA/DCD/031/USA which was used at the meeting. Capt. Short called back later in the day to clarify several items discussed at the 12/20/94 phase II meeting.
22 Dec 94	Letter	Non-official submission of cleaner copy of serum glucose overhead as part of presentation at 12/20/94 phase II meeting. Also, names and titles of Novo Nordisk's representatives at meeting were sent to FDA (Capt. Short) per as a follow-up to telephone request of 12/22/94.
31 Jan 95	030	Protocol Amendment: provides for 2 new investigators (John Hunt and Hugh Tildesley)
14 Feb 95	031	Protocol Amendment: provides for 1 revised investigator (Robert G. Brodows) 1572.
15 Feb 95	Phone	Telephone call to FDA (John Short) to advise them of Canada's HPB action regarding their refusal to remove the hold placed on study AGEE/DCD/049/USA. The reason for HPB's concern is over preliminary results of rat carcinogenicity study 46Q.
15 Feb 95	032	Information Amendment - Clinical. Written notification regarding Canada's HPB actions regarding suspension of enrollment for 3 Canadian investigators and procedures implemented to withdraw patients from protocol AGEE/DCD/049/USA. The reason for

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
		HPB's concern was over preliminary results of rat carcinogenicity study 46Q.
6 Mar 95	Phone	FDA Pharmacology reviewer (Dr. Rhee) telephoned to ask if we had submitted reports from the rat and mouse carcinogenicity studies to the IND. He was advised that the final study reports should be available June/July of this year and at that time, the reports would be submitted to the IND. Dr. Rhee commented that the Canadian HPB had put the clinical investigation on hold; he was informed that FDA was informed about this matter via phone and via submission (serial no. 032). Dr. Rhee then inquired as to whether we had submitted the intended doses for the carcinogenicity studies to FDA for comment prior to the start of the study. He was advised that we had not done so but that Dr. Jordan stated that he was satisfied with the conduct of these studies based on the data provided at the end of the Phase II meeting.
7 Mar 95	033	Information Amendment: Response to questions raised at the end of the Phase II meeting held on 12/20/94 regarding the pivotal Phase II efficacy studies, AGEE/DCD/037/USA (being conducted in the US) and AGEE/DCD/028/NL (being conducted in Europe), and the definition of efficacy in study AGEE/DCD/028/NL which utilizes an approved active (rather than a placebo) control.
5 Apr 95	034	Protocol Amendment: provides for a change in protocol AGEE/DCD/049/USA and a new investigator (Stuart Weiss).
10 Apr 95	035	Information Amendment - Clinical. Provides copies of final study reports for Study USA/OHA/059/AG (AGEE/DCD/9/USA) and Study AGEE/DCD/031/USA.
17 Apr 95	Phone	FDA (Michael D. Jones) was contacted to obtain information on what the environmental assessment requirements would be in an NDA for AGEE 623 ZW (repaglinide) tablets. Mr. Jones was advised that an EA was being planned according to the EEC directives, NNPI inquired as to whether such a document would suffice as an EA for the NDA which is planned for submission in approximately 18 months. Mr. Jones indicated that the White House has recently recommended elimination of the EA as part of the NDA requirements and that he did not know what the results of this would be in 18 months. Mr. Jones was unwilling to make a commitment regarding whether an EA would or would not be required when the NDA for repaglinide is submitted.
20 Apr 95	Phone	FDA (Dr. Rhee) telephoned with additional questions concerning our carcinogenicity studies. He indicated that our protocols were good but that they had not seen study reports which he believed we had submitted to HPB. He was advised that the study reports were still being prepared and that they would be provided to him when they became available in June/July 1995 (Dr. Rhee also telephoned in March with the same questions and he was provided with the same answer as above.) Dr. requested copies of several other documents which had been previously submitted (serial no. 036) stated that he was behind in his review.
21 Apr 95	036	Submission of desk copies of: (a) IND Serial No. 025 (dated November 21, 1994) and, (b) Overheads of preclinical study results which were presented at a December 21, 1994 end of Phase II meeting with the Agency. These documents were provided as a follow-up to an April 20, 1995 telephone call from Dr. Rhee, Pharmacology Reviewer.
21 Apr 95	037	Request for a meeting with the Agency to discuss draft design of protocols for a dose response study and long-term placebo-

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
		controlled safety study. Reference is made to an end of phase II meeting held December 20, 1994 and an April 21, 1995 telephone conference with John Short (CSO). In the December meeting Dr. Gueriguian indicated that Novo Nordisk should conduct another dose response study as well as a long-term placebo-controlled safety study; (Dr. Gueriguian asked that prior to initiation of these studies, we should discuss the protocols with him.)
8 May 95	038	Protocol Amendment: provides for a new Phase I clinical pharmacokinetics study under protocol AGEE/DCD/057/USA to be conducted by Jerry M. Herron, M.D.
10 May 95	039	General Correspondence: Reference to May 4, 1995 telephone conversation with John Short (CSO) in which a June 8, 1995 meeting date was set to discuss the protocols for conducting studies of dose response and long-term safety. Copies of the study designs for discussion were provided to Capt. Short for distribution to the Agency personnel who will be attending the meeting.
12 May 95	040	Submission of IND Progress Report for time period March 1994 through February 1995.
18 May 95	Phone	FDA (Dr. Rhee) telephoned with additional questions regarding the status of the carcinogenicity study and maximum tolerated dose (reference is made to amendments 005 and 025). Also requested AUC information relating to carcinogenicity study and dose levels. F. Longenecker/M. Herzig to follow-up..
19 May 95	Phone	F. Longenecker followed-up on FDA-initiated May 19, 1995 telecom with FDA (Dr. Rhee). Dr. Rhee was advised that the study reports for the two carcinogenicity studies were expected in June-July 1995 (this information was provided to him on two previous occasions). He was also advised that the AUC data for clinical dosing and from the two carcinogenicity studies verified that there was a greater than 25 fold difference between human and animal values (at the top dose). Dr. Rhee was advised that this information had been provided at the December 20, 1994 end of Phase II meeting as well as in IND Amendment no. 36.
25 May 95	041	Amendment to IND Progress Report (Serial No. 040, dated May 12, 1995): Additional information for section 312.33(b)(3) List of Deaths was submitted regarding a death which occurred in The Netherlands.
1 June 95	042	General Correspondence: Reference is made IND Serial No. 005 and to a May 19, 1995 telephone call between Dr. Hee M. Rhee (Pharmacology Reviewer) and F. Longenecker in which Dr. Rhee commented on the body weight reduction seen in a 13-week dose-range finding study in mice (study 32Q) when compared to that seen in the 2-year carcinogenicity study (study 450525).
9 June 95	Memo	FDA's Memorandum of End-of-Phase 2 Meeting held December 20, 1994.
9 June 95	043	IND Safety Report for a serious adverse event (mfr. 95/1489) which occurred during a phase III study (AGEE/DCD/047/F) with repaglinide.
15 June 95	044	Information Amendment which provides results of clinical investigations with subject drug. In addition, a copy of the final study

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
		report from protocol B/OHA/038/AG (also designated AGEE/DCD/005/B) was enclosed.
11 June 95	045	General Correspondence: Submission of Novo Nordisk minutes for the June 8, 1995 meeting; additionally, a request was made for a copy of FDAs meeting minutes.
22 June 95	Memo	Novo Nordisk minutes of June 8, 1995 meeting at FDA to reach agreement on the design of two studies (dose-response and long-term safety) which Novo Nordisk planned to conduct as a result of requests from FDA at the December 20, 1994 end of phase II meeting.
22 June 95	Memo	Addendum to minutes of June 8, 1995 meeting at FDA (Ref. 6/22/95 memo). FDA (Dr. Fossler) asked if NNPI (Dr. Perentesis) planned to perform mixed effect computer modeling in evaluating the data from the dose-response study. NNPI (G. Perentesis) stated that we did not think that we were planning to do this modeling; Dr. Fossler asked if for permission to do the work and to present a paper on it.
26 June 95	046	IND Safety Report for a serious adverse event (mfr. 95/1625) which occurred during a phase III study (AGEE/DCD/050/D) with repaglinide.
19 July 95	047	Protocol Amendment which provides for revised investigator information (delete Jay M. Sosenko as co-investigator and name Ronald B. Goldberg as sole principal investigator).
19 July 95	048	IND Safety Report for a serious adverse event (mfr. 95/1844) which occurred during a phase III study (AGEE/DCD/049/USA) with repaglinide.
2 Aug 95	049	Protocol Amendment which provides for revised investigator information (change of address for Thomas C. Blevins, MD).
4 Aug 95	050	IND Safety Report: Follow-up to Initial Written Report, Amd. No. 043 dated 6/9/95, (mfr. no. 95/1489), for a serious adverse event which occurred during study AGEE/DCD/047/F).
23 Aug 95	051	General Correspondence: Submission of proposed stability plan (A proposed stability protocol of registration application of repaglinied (AGEE 623 ZW) tablets (0.5, 1.0, 2.0 mg) for review and comments from Dr. Yuan Yuan Chiu, FDA Supervisory Chemist review and comments
11 Sept 95	052	Protocol Amendment which provides for revised investigator information for Drs. Thomas C. Marbury & John H. Shelmet for participation in study AGEE/DCD/049/USA.
18 Sept 95	53	Information Amendment: provides final study reports on additional nonclinical pharmacology and toxicology studies 50525 and 46Q in addition to two special segment III reproduction toxicology studies (window study - 42R & influence of modulators study - 70R). Ref. additionally made to 11/21/94 amd. serial no. 025 and 5/19/95 telecom.

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
2,3 Oct 95	TCR	On 10/2/95 a call was made to FDA (Dr. Chiu) to follow-up on Amd. Serial No. 051 in which a request for comments on a stability protocol prepared by Thomae for the repaglinide NDA. Dr. Chiu stated that she had looked over & sent the protocol to Dr. Ysern (chemistry reviewer) for his comment. On 10/3/95, during a telecom with Dr. Ysern, he indicated that 3 dosage strengths should be included in the protocol; Dr. Chiu indicated that 2 lots of each strength were sufficient. Dr. Ysern agreed with this. It was also noted that Dr. Chiu had indicated that two lots of each strength were sufficient, Dr. Ysern stated that he would have to have to discuss with Dr. Chiu prior to sending a written reply.
16 Oct 95	054	Protocol Amendment provides for a new Phase I clinical pharmacokinetics study under protocol AGEE/DCD/040/USA to be conducted by Thomas C. Marbury, M.D.
20 Oct 95	055	IND Safety Report - Second Follow-up for a serious adverse event (mfr. report no. 95/1489) which occurred during protocol study AGEE/DCD/047/F. The initial report was submitted on 6/9/95 (serial no. 043) and the first follow-up was submitted on 8/4/95 (serial no. 050).
20, 23 Oct 95	TCR	FDA (Dr. Rhee) telephoned with a request that we provide the data for oncogenicity studies 450525 and 46Q (submitted in Amendment Serial No. 053, dated 9/13/95) on disk for statistical review. Following consultation with NNAS (M. Kock) & Consultant (Fred Reno), FDA (Drs. Rhee and Lin were contacted to advise them that the data would be provided to them on a disk but that it would take a while to compile the disk.
30 Oct 95	TCR	FDA (Capt. John Short) was contacted to inform them that a patient in our phase III trial (AGEE/DCD/049/USA) had killed his wife with a baseball bat. FDA was also informed that the patient was divorced from his wife at the time of the event, had a history of spousal abuse and that his wife had had a restraining order issued on him. NNPI has reason to believe that the defendant would claim that hypoglycemia (and/or repaglinide) was the cause of his behavior. NNPI felt that it was prudent to notify the Agency so that they would not be caught unaware. Capt. Short requested that this information be submitted to the IND.
3 Nov 95	TCR	As follow-up to previous telephone discussions (10/2 & 3/95), FDA (Dr. Ysern) was contacted to clarify the previously unresolved issue of container sizes to be incorporated into the stability program. Dr. Ysern has three comments regarding the stability program and indicated that he would put these comments in writing by the end of the following week and send them to NNPI.
10 Nov 95	056	Protocol Amendment which provides for revised investigator information for Dr. Stuart Weiss for participation in study AGEE/DCD/049/USA.
20 Nov 95	057	Information Amendment which provides revised drug product release and stability specifications/analytical methods for 4 dosage

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

DATE	CONTACT TYPE	DESCRIPTION
		strengths.
21 Nov 95	058	Protocol Amendment which provides for a new Phase II clinical pharmacokinetics study - AGEE/DCD/064/USA - and form FDA 1572 and CV for principal investigator Dr. Thomas Marbury.
28 Nov 95	059	IND Safety Report for a serious adverse event (mfr. control no. 95/3203) which occurred during a Phase III study (AGEE/DCD/050/D) conducted in Germany.
4 Dec 95	TCR	As follow-up to 10/30/95 telephone conversation with FDA (Capt. Short), additional information was provided on the subject case. FDA was advised that the defendant was found guilty and was being sentenced to 25 years to life. The jury had not found any connection between the defendant's actions and his use of repaglinide in clinical trial AGEE/DCD/049/USA.
6 Dec 95	060	IND Safety Report for a serious adverse event (mfr. control no. 95/3247) which occurred during a Phase III study (AGEE/DCD/049/USA) conducted in the US.
18 Dec 95	061	Protocol Amendment which provides for a new Phase III clinical safety study - AGEE/DCD/065/USA - and form FDA 1572 and CV for principal investigator Dr. Robert G. Brodows.
22 Dec 95	062	Protocol Amendment which provides for new investigators Drs. Ronald Goldberg, Ronald Graf, William Polvino, Sherwyn Schwartz and Irving Weston for participation in study AGEE/DCD/064/USA.
22 Dec 95	063	General Correspondence - Teleconference Request. (Reference is made to 12/20/94 Phase II meeting in which several items including the nonclinical animal studies for submission in the NDA were discussed.) FDA (Dr. Jordan to be contacted the week of January 8, 1996 to set up a teleconference later in the month.

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

16, 17 Jan 96	TCR	FEL contacted Dr. A. W. Jordan on 1/16 to set up teleconference including F. Reno (xref: serial 063) to discuss NNPI proposal of submitting all studies conducted with repaglinide & four racemate studies (instead of all) to NDA since NNPI was conducting studies since 12/95 with the former to take the place of racemate. He asked for time to re-review the IND and called back on 1/17 to inform that he agrees with NNPI proposal, that it is adequate to support an NDA and we did not need to include other racemate studies. Asked that we make reference to this conversation in our NDA.
25 Jan 96	Memo	RE: June 8, 1995 Repaglinide meeting. Copy of FDA minutes from clinical meeting (background material contained in 5/10/95 submission. Meeting discussion centered on design of dose-response & long-term placebo safety study.
25, 26 Jan 96	TCR	On 1/25/96, John Short, CSO (FDA) telephoned with a comment from Dr. Gueriguian on the subject study. A telephone conversation with Dr. Gueriguian later in the day indicated that his concern was whether or not the size of the daily dose (12 mg) or the length of dosing (6 months) was "novel". Dr. Gueriguian was advised that it was probable that in our ongoing phase III studies we have patients who had been treated at this dose level for this length of time. He further indicated that he wanted Novo Nordisk clinicians to verify this and set up a telephone conference for the following day. On 1/16/96, a three-way telephone conference between NNPI, NNAS and Dr. Gueriguian; Dr. Gueriguian stated that after reading protocol AGEE/DCD/065/USA, he could not tell whether we have past experience administering the 4 mg TID dose to patients for the length of time proposed. He was informed that of the 1354 patients enrolled in phase III trials more than 50% were at dosage level 4 corresponding to 4 mg TID. Dr. Gueriguian asked that we send this information in a letter.
29 Jan 96	064	General Correspondence: Ref. is made to serial No. 061 (dated 12/13/95) and telephone conversation 1/26/96 with Dr. John Gueriguian, FDA medical reviewer. Serial no. 061 provided a protocol for a 6-month fixed dose safety study (065) which provided for a placebo, 1 mg repaglinide TID and 4 mg TID dose level. In 1/26/96 telephone conversation, the results of five 1-year phase II studies were related to Dr. Gueriguian and he requested that this information be put in writing; this submission is in response to that request.
1 Feb 96	065	Protocol Amendment which provides for new investigators Drs. Thomas C. Marbury and Irving Weston for participation in study AGEE/DCD/064/USA.
15 Feb 96	ROC	S. Maloney contacted K. Srinivasachar (FDA) regarding amount of stability data required for new NDAs. Effective Jan. 1, 1998, all original NDA applications to contain 12 month RT stability data. For now FDA would like that up front but negotiable. Minimal acceptance is 6 months RT data with written commitment that remainder of data will be submitted prior to completion of review, i.e., remaining 6 months data should be submitted with the 4 month safety update.
22 Feb 96	066	Protocol Amendment which provides for new investigators Drs. Sheldon Berger, George E. Dailey, Charles Kilo, David A. Podlecki, Julio Rosenstock and Stuart Weiss for participation in study AGEE/DCD/065/USA.
23 Feb 96	067	Information Amendment: CMC amendment to provide revised drug product manufacturing methods for the 0.5 mg, 1.0 mg and 2.0 mg tablets.

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

27 Feb 96	068	Information Amendment: Pharmacology/Toxicology amendment to provide requested diskettes formatted according to NTIS document #PB9D-213885 as requested by Dr. Lin (10/23/95). Studies regarding the tumor data is provided; body weight, food consumption and organ weight data are not included. Full data files will be provided when the studies are submitted in an NDA for repaglinide). **(Ref. Amd. Serial No. 053 dated 9/12/95 and telephone contacts on 10/23/95 and 11/27/95 with Dr. Rhee and Dr. Lin.)**
11 Mar 96	069	IND Safety Report -Follow-up to Initial Safety Report (serial no. 060 dated 12/6/95) providing revised information in items 5 and 6.
13 Mar 96	Letter	Certified Mail from FDA (Dr. Viswanathan) requesting all of the histologic tissue sections of thyroid, liver, and uterus/testes from all animals in all dose groups, as well as control animals from Study #46Q - "Carcinogenicity Study in Rats by Oral Administration (Dietary Admixture) Over a Period of 24 Months".
18 Mar 96	TCR	Telephoned FDA (Dr. Peters) to inquire further into the request made by Dr. Viswanathan on 3/13/96 and to ask if there was a specific issue of concern; we were advised that this was a routine request. Dr. Peters stated that she was asked for her input for Dr. Rhee's review and that she needed to review the slides in order to provide input.
19 Mar 96	070	Protocol Amendment which provides for new investigators Drs. Rober J. Anderson, Thomas Blevins, Arthur Green, George Grunberger, Serio R. Mather, Sam S. Miller, Lois Jovanovic-Peterson, Sanford N. Plevin and Robert Ratner and revised investigator for Dr. Julio Rosenstok -- all for participation in study AGEE/DCD/065/USA.
26 Mar 96	FAX	FDA (Ms. Rhee) requested that the Informed Consent Form submitted in IND Information Amd. Serial No. 053, dated 9/18/95, be modified to include the following: "Mice and rats receiving doses of AG-EE 623 (repaglinide) 1000-3000 times the proposed maximum human dose for 2 years developed an increased incidence of mammary gland carcinoma and hepatic adenomas."
29 March 96	TCR	FDA (Ms. Rhee) was contacted and advised that NNPI questioned whether the proposed FDA statement (which was requested March 26, 1996 via telefax) was intended for repaglinide and was advised of the inconsistencies between the requested changes to the informed consent forms and the study results. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
1 Apr 96	TCR	FDA (Ms. Rhee) telephoned to say that she had discussed the issue with Dr. Herman Rhee and he said that he did intent for use to revise our informed consent form. He did nidicate that we could delete the reference to mice. Ms. Rhee was told that there were other inconsistencies which needed to be addressed and NNPI had an alternate wording; Ms. Rhee stated that she would discuss it with Dr. Rhee and he would call back. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
1 Apr 96	TCR	FDA (Dr. Rhee) telephoned and an alternate statement for use in the informed consent form was read to him and he requested that the statement be telefaxed to him and he would discuss it with Dr. Jordan. Dr. Rhee called back with modifications to the ICF. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

1 Apr 96 (11:35am)	FAX	Follow-up to TCR of 4/1/96 regarding statement for Informed Consent Form; submission of alternate wording for the statement which was requested by FDA (Dr. Rhee).
1 Apr 96 (1:16 pm)	FAX	Second follow-up to TCR of 4/1/96 requesting further revisions to statement for Informed Consent Forms for use in clinical studies with repaglinide.
2 Apr 96	TCR	FDA (Dr. Rhee) was contacted and asked if the most recent statement (sent at 1:16 pm on April 1) for the informed consent form was acceptable. After some discussion, Dr. Rhee agreed that the wording in the latest version (sent April 1 at 1:16 pm) was acceptable. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
3 Apr 96	TCR	FDA (Ms. Rhee) called and requested that NNPI send her a hard copy of the thrid statement (submitted April 1 at 1:16 pm) for inclusion in the informed consent form. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
8 Apr 96	TCR	FDA (Ms. Rhee) was contacted and informed that NNPI requested a telephone conference with her, Dr. Rhee and Dr. Alexander Jordan to further discuss the issue of adding a statement to the informed consent. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
10 Apr 96	TCR	A follow-up call was made to FDA (Ms. Rhee) to find out if a date for a teleconference had been confirmed. A date of April 24 (3:30) was set for the teleconference. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
12 Apr 96	071	Protocol Amendment which provides for a new investigator (Dr. Jon Ruckle) for participation in study AGEE/DCD/040/USA and new investigators (Drs. Leslie J. Klaff, Arthur Krosnick and James H. Mersey) for participation in study AGEE/DCD/065/USA.
16 Apr 96	072	Information Amendment - Pharmacology/Toxicology. Submission of requested slides of all histologic tissue sections of thyroid, liver and uterus/testes from all anaimals in all dose groups, as well as control animals from Study #46Q.
24 Apr 96	TCR	Teleconference with FDA (Dr. Jordan, Dr. Rhee and Ms. Rhee - FDA) and NNPI (Dr. Reit, Dr. Whisnant, Mr. Hooker and Mr. Longenecker) to further discuss FDA's request for inclusion of a statement in the informed consent form concerning observations from the rat carcinogenicity study. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
29 Apr 96	TCR	FDA (Dr. Rhee) telephoned and asked where the report by Dr. Squires was located. He was advised that it appeared in volume 22 of IND 39,012, Serial No. 053, submitted September 18, 1995. Dr. Rhee stated that he was unable to find it and asked that an additional copy be sent to him. (Desk copy (Amd. No. 073) sent April 30, 1996. **(SEE RECORD OF CONTACT DATED MARCH 26, 1995 THROUGH APRIL 29, 1996.)**
30 Apr 96	073	Response to FDA request for information: Submission of additional copy of volume 22 (pages 6076-6272) of serial no. 053 (dated September 18, 1995) in response to Dr. Rhee's (FDA pharmacology reviewer) request on April 29, 1996.
14 May 96	074	Protocol Amendment: Submission of two new Phase I clinical safety studies: AGEE/DCD/070/USA and AGEE/DCD/069/USA including submission of CVs and 1572s for new principal investigators Thomas J. Christopher and Albert Cohen.

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

22 May 96	TCR	FDA (Dr. A. Jordan, supervisory toxicologist) was contacted to follow-up on April 25, 1996 teleconference, in which Dr. Jordan had agreed to review the report by Dr. Squires, which had been included in IND Amd. Serial No. 053, dated September 8, 1996. Dr. Jordan indicated that he had some concerns over the statement about effects on thyroid hormones in rats not being expected in humans. Conversation concluded with Dr. Jordan stating that he is still looking at the issue and will discuss it with Dr. Sobel.
7 June 96	FAX	FDA requested that a paragraph about rodent carcinogenicity results be inserted in the informed consent form (reference is made to protocol amendment #053, dated September 18, 1995).
14 June 96	FAX	NNPI responded to FDA's FAX dated 7 June 96 and presented an alternate statement to FDA s June 7 statement regarding the rodent carcinogenicity results which are to be included in the informed consent forms.
30 May 96	075	Protocol Amendment which provides revised investigator information for Dr. Ronald J. Graf for participation in study AGEE/DCD/064/USA and new investigator information for Dr. Barry J. Goldstein for participation in study AGEE/DCD/065/USA.
5 June 1996	076	IND Safety Report: Follow-up to Initial Safety Report (Amd. Serial No. 059) submitted on November 18, 1995.
6 June 96	077	General correspondence: Reference is made to meetings held on 12/20/94 and 6/8/95 and to IND amendment numbers 019 and 061. This correspondence presents two proposals for which the Agency is requested to provide comments on Phase III statistical analysis and a six month safety study.
7 June 96 & 14 June 95	TCR	June 7: FDA sent a telefax to NNPI which provided a statement which the Agency was requiring NNPI to add to the informed consent forms for repaglinide clinical studies. June 14: FDA was provided with an alternate statement to be added to the informed consent form
25 June 96	TCR	FDA (Dr. Baldeo Taneja) telephoned to request clarification of page 5, Statistical Analysis Plan, Protocol AGEE/DCD/046/UK. Corrected page was FAXED to FDA (original submission had a sentence missing.)
27 June 96	078	IND Safety Report - Second Follow-up for a serious adverse event (initial report submitted in Amd. Serial No. 059 dated November 28, 1995; 1st follow-up submitted in Amd. Serial No. 076 dated June 5, 1996) which occurred during a Phase III study (AGEE/DCD/050/D) conducted in Germany.
10 July 96	FAX	NNPI requested a 15-30 minute teleconference to discuss the issue of the weight of evidence that the Agency will give to NNPI's 5 one-year active control (comparator) studies.
10 July 96	TCR	FDA informed NNPI that the requested teleconference was not necessary (Dr. Baldeo Taneja had approved our statistical plan and Dr. Gueriguian had agreed to our submission proposal). NNPI again requested time with FDA to further discuss the weight of evidence which would be given to the five active comparator clinical studies to be submitted in the repaglinide NDA as support of efficacy.

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

11 July 96	TCR	Teleconference was held to discuss the five active comparator clinical studies. It was concluded that (1) NNPI will submit placebo controlled study 033 in the original NDA, (2) active comparator studies 046, 047, 048, 049 and 050 will be submitted in the original NDA, and, (3) placebo controlled study 065 will be submitted as partial data. A final study report will be submitted at the 120-day safety update to the NDA.
17 July 96	079	IND Safety Report - Third follow-up to an initial Safety Report (Amd. Serial No. 043 dated June 9, 1995), 1st follow-up report (Amd. Serial No. 050 dated August 4, 1995) and second follow-up report (Amd. Serial No. 055 dated October 20, 1995) for a serious adverse event which occurred during study AGEE/DCD/047/F.
15 Aug 96	080	IND Safety Report - initial report for a serious, unexpected event of hypertriglyceridaemia, condition aggravated which occurred in a 49 year old male in France while participating in Protocol AGEE/DCD/47/F (mfr. control no. 96/2097).
16 Aug 96	081	IND Safety Report - Second follow-up report to initial safety report (serial no. 060) submitted 12/6/95 and first follow-up report (serial no. 069) submited 3/11/96 for mfr. control no. 95/3247.
21 Aug 96	082	IND Safety Report - initial report for a serious, unexpected event of a suicide attempt which occurred in a 65 year old female in Germany while participating in Protocol AGEE/DCD/50/D (mfr. control no. 95/1625). **(NOTE: this report was incorrectly submitted as initial report; correction submitted in serial no. 083 submitted 8/30/96.)**
23 Aug 96	ROC	FDA (Dr. Guo) telephone to report that the diskettes of tumor data for carcinogenicy studies 46Q (rats) and 450525 (mice) previously submitted in February were not in the correct format and requested that the diskettes that we redo the diskettes using the DOB format.
30 Aug 96	083	IND Safety Report - Second follow-up report to initial safety report (serial no. 046) submitted 6/26/95 and first follow-up report (serial no. 082) submitted 8/21/96 for mfr. control no. 95/1625.
25 Sept 96	084	Protocol Amendment which provides revised investigator information for Drs. George Dailey and Charles Kilo for participation in study AGEE/DCD/049/USA and revised investigator information for Drs. Charles Kilo, Stuart Weiss, Julio Rosenstock and Barry J. Goldstein for participation in study AGEE/DCD/065/USA.
1 Oct 96	085	IND Safety Report - follow-up report to initial safety report (serial no. 080) submitted 8/15/96 for mfr. control no. 96/2097.
2 Oct 96	086	Annual Progress Report for time period March 1, 1995 through February 29, 1996.
3 Oct 96	087	IND Safety Report - initial report for a serious, unexpected event of cholelithiasis which occurred in a 52 year old female in Belgium while participating in Protocol AGEE/DCD/47/B (mfr. control no. 96/2638).
10 Oct 96	ROC	RE: Pre-Approval Promotion. FDA Mike Johnston, CSO) was contacted to request a teleconference with Drs. John Gueriguian and A. Gilbert Flemming to discuss a safety trend in cardiovascular events seen in study AGEE/DCD/049/USA. (A table of cardiovascular events from this study was telefaxed to FDA along with four questions and a request for a teleconference that

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

		same day.)
10 Oct 96	FAX	RE: IND 39,012 - Repaglinide Tablets (oral hypoglycemic agent) - Safety. Follow-up to telephone conversation today with FDA (Michael Johnston, CSO) in which NNPI requested a teleconference with Drs. Gueriguian and Flemming to discus questions based upon table 34 entitled "Cardiac Treatment Emergent Adverse Events" from clinical trial AGEE/DCD/049/USA.
21 Oct 96	088	IND Safety Report - follow-up report to initial safety report (serial no. 087) submitted 10/3/96 for mfr. control no. 96/2638.
22 Oct 96	ROC	FDA (Dr. Xavier Ysern, chemistry reviewer) was contacted to inquire about batch records to be included in the NDA. Dr. Fossler, FDA biopharmaceutics reviewer was also contacted to find out if NNPI was required to conduct bioequivalence studies. As as result of the conversations with Drs. Ysern and Fossler,Thomae will provide untranslated and translated master and completed batch records for each tablet strength (o.5, 1.0 and 2.0 mg), NNAS will compile CMC portion of NDA as per Dr. Ysern's comments and will conduct dissolution studies if uncolored tablets are used for phase IIIb/IV studies.
7 Nov 96	FAX	FDA (Mike Johnston, CSO) sent comments on submissions dated 9 Sept 95 and 23 Aug 95 (Amd. 051 and reference to October 3, 1995 telecom with Dr. Ysern, FDA).
8 Nov 96	FAX	Follow-up to October 10, 1996 telephone and fax communications with FDA (Mike Johnston, CSO) again requesting a teleconference or face-to-face meeting with Drs. Gueriguian and Flemming to discuss questions based upon the tables/figure from study 049/USA.
12 Nov 96	089	General Correspondence - Safety: Meeting request to discuss initial safety data from U.S. phase III trial AGEE/DCD/049/USA (ref. made to Oct. 10, Nov. 8 and Nov. 12 telephone contacts).
13 Nov 96	FAX	RE: Stability protocol which was sent to Dr. Ysern on Nov. 6, 1996 and the difference in several points from that which was designed based upon previous discussion with Dr. Ysern.
17 Nov 96	FAX	FDA sent FAX referencing August 23, 1996 phone conversation with FDA (Dr. Guo) regarding the status of the data for carcinogenicity studies (450575 and 46Q) in which NNPI agreed to resubmit the data using the DOB data format. This correspondence from Dr. Guo also inquired about the status of the data.
18 Nov 96	ROC	A phone message was left for FDA (Dr. Guo) advising him that the diskettes had been received and would be sent out to him either today or tomorrow (reference August 23, 1996 ROC and November 17, 1996 FAX).hone and
19 Nov 96	FAX	FDA■s Memorandum of Telecon regarding cardiovascular adverse events review following comments from Dr. John Gueriguian after review of the telefax submission of October 10, 1996; this information was also submitted to the Agency as an official submission within the past week.
20 Nov 96	090	Information Amendment - Pharmacology/Toxicology. Ref. to amendment serial no. 068 submitted Feb. 27, 1996 which provided the tumor data on diskettes as requested by Dr. Lin (Oct. 23, 1995) and telephone contacts on Aug 23, 1996 with Dr. Guo in which a request was made to reformat the data into the DOB format. This submission provides one set of diskettes which have

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

		been formatted into the DOB format and a four-page printout of the "DOB Data Formats for carcinogenicity studies".
20 Nov 96	091	Protocol Amendment which provides revised investigator information for Dr. Thomas Blevins for participation in study AGEE/DCD/049/USA and Dr. Sherwyn Schwartz for participation in study AGEE/DCD/064/USA.
27 Nov 96	ROC	FDA (Mike Johnston, FDA-CSO) was contacted and advised that NNPI had received his telefax of responses from Dr. Gueriguian to the CV safety data from study 049/USA. He was told that, as recommended, NNPI was contacting consultant cardiologists to discuss the 049/USA data and obtain their opinions. Further, he was advised that a pre-meeting package was being prepared to submit and that a request for a meeting to discuss various clinical efficacy/safety issues as well as format issues for the clinical section of the NDA for repaglinide. Discussions centered around NNPI's request for a meeting; Mr. Johnston called back and left a message that he had tentatively set a meeting date of January 23, 1997 for the meeting.
10 Dec 96	ROC	Reference made to Oct. & Nov. 1995 telephone discussions with FDA (Dr. Ysern) regarding Novo Nordisk (Thomae) proposals for the repaglinide NDA batch stability program. Based upon these discussions (re. To ROCs for Oct. 2 & 3 & Nov. 3, 1995) the stability program was revised, initiated and is currently under way. On Nov. 11, 1996, FDA telefaxed comments on the stability program to NNPI. These comments differed from those which Dr. Ysern had agreed to earlier. After further discussions with FDA, it was agreed that the Novo Nordisk program would be okay since we would have data on all strengths and would have data for all containers at the longest time in the program.
13 Dec 96	092	General Correspondence - Clinical Meeting Request. Novo Nordisk requests a meeting with FDA to discuss the clinical portion of NDA 20-741; a tentative date of Thursday, January 23, 1997 was set for this meeting in a November 27, 1996 telephone communication with FDA (Michael Johnston, CSO).
13 Dec 96	093	Information Amendment - Chemistry. Reference made to information amendment serial no. 051 submitted Aug 23, 1995 and to a series of communications between FDA (Dr. Xavier Ysern) and Novo Nordisk (Fred Longenecker) regarding amendment serial no. 051 which provided a drug product stability program proposal for discussion with the agency. It has been agreed with FDA (Dr. Ysern) that the ongoing stability program is acceptable for an NDA for repaglinide and this correspondence confirmed the above.
13 Dec 96	TCR	Ms. C. Williamson (FDA) contacted L. Joesten requesting that representative labeling for all Danish manufactured products be sent to Drug Listing Office. Request in connection with changing of labeler code for Danish mfg. site. Ms. Joesten stated that Mr. L. Lim, had stated labeling is not required when there are no changes on labels-- Ms. Williamson requested that we send an authorization letter on NNAS letterhead stating NNPI is authorized to represent NNAS in handling all drug listing & regulatory issues.
20 Dec 96	094	IND Safety Report - follow-up report to an initial safety report, mfr. control no. 95/1844 (amendment serial no. 048) submitted July 19, 1995.
23 Jan 97	095	IND Safety Report - second follow-up report to an initial safety report mfr. control no. 96/2638 (amendment serial no. 087 submitted on 10/03/96; and first follow-up report amendment serial no 088 submitted on 10/21/96).

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

23 Jan 97	ROC	Minutes of January 23, 1997 meeting held at FDA, Metabolism Endocrine Division to discuss the clinical portion of upcoming NDA for repaglinide.
27 Jan 97	ROC	Phone contact was made to FDA (Dr. Herman Rhee, nonclinical pharmacology reviewer) to ask him about inclusion of references within the nonclinical section of the upcoming NDA. NNPI (F. Longenecker) indicated to Dr. Rhee that the nonclinical studies which would be submitted to the NDA had numerous citations to study and literature documents and NNPI wanted to discuss how to handle them in the references section of the NDA.
30 Jan 97	ROC	FDA (Dr. Misbin) telephoned on January 29, 1997 on an insulin item and at the end of the call he commented that he had enjoyed NNPI's repaglinide clinical meeting and thought the information was well presented. Dr. Misbin added that he thought that a combination of repaglinide with acarbose was an interesting possibility due to their different mechanisms of action and their similar dosing schedules.
7 Feb 97	096	General Correspondence: A copy of NovoNordisk's minutes of January 23, 1997 meeting to discuss clinical issues in preparation for submission of an NDA was submitted as general correspondence. Also a request was made that the division indicate whether it concurs with these minutes and forward a copy of the official division minutes to Novo Nordisk when available.
10 Feb 97	ROC	A telephone call was made to FDA (Anne Reb, Division of Drug Marketing, Advertising and Communication) on 2/7/97. Reference was made to a previous conversation (10/96) with Ken Feather (DDMAC senion advisor) regarding prmotional pre-approval activities and the use of abstracts (NNPI planned to use them at the upcoming ADA convention to be held June 24-26, 1997.)
11 Feb 97	ROC	F. Longenecker agreed to provide data disks, in CD-ROM format, to Dr. Taneja (demographics, safety, efficacy for the 9 studies identifiedas substantial evidence of safety and efficacy) and Dr. Fossler (data only on those studies which NN believed would be most improtant for his review) within two months of the submission of the NDA.
15 Feb 97	ROC	S. Maloney contacted K. Srinivasachar (FDA) regarding amount of stability data required for new NDAs. Effective Jan. 1, 1998, all original NDA applications to contain 12 month RT stability data. For now FDA would like that up front but negotiable. Minimal acceptance is 6 months RT data with written commitment that remainder of data will be submitted prior to completion of review, i.e., remaining 6 months data should be submitted with the 4 month safety update.
19 Feb 97	FAX	FDA (Julie Rhee, CSO) requested additional data/information in formats of tables or figures on (1) the major metabolites of repaglinide in rats, mouse, dogs and man with % of their recovery (ADME data), (2) what were the document number(s) of one-year toxicity studies in dogs and rats?, (3) requested exposure ratios (animals to huma0 based on AUC for several studies, (4) AUC values in individual animals which exhibited frank toxicity, if available, and (5) data on protein binding in test species and human.
25 Feb 97	097	IND Safety Report - Third follow-up report to an initial safety report, mfr. control no. 95/3203 (amendment serial no. 059 submitted on 11/28/95; first follow-up report amendment serial no. 076 submitted on 6/5/96and second follow-up report

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

		amendment serial no. 078 submitted 6/5/96).
24 Feb 97 28 Feb 97	ROC	**2/24/97**: On 2/10/97 FDA (Julie Rhee, CSO) sent a telefax to NNPI (B. Reit) requesting various preclinical information for Dr. Herman Rhee, nonclinical pharmacology reviewer. NNPI (F. Longenecker) telephoned Ms. Rhee on 2/24/97 and provided the answer to 2 items and requested that the remaining 4 questions be answered in the NDA which would be submitted in the near future. Ms. Rhee stated that she would ask Dr. Rhee and call back with an answer. **2/28/97**: FDA (Julie Rhee, CSO) called back to say that Dr. Rhee wanted NNPI to send him what information we had at this time and send the rest later.
18 March 97	098	Preclinical Toxicology Information Amendment: Responses to FDA questions and toxicokinetic study 70S submission.
20 March 97	099	A minor typograhical error was noted in the dose level for study 46Q in Table 4 on page 7. Page 7 of the original report should be replaced by the corrected page 7 which was enclosed. (Ref. serial no. 098, 3/18/87 submission).
25 March 97	FAX	Meeting minutes of Ja uary 23, 1997 meeting between FDA and NNPIregarding Pre NDA review of clinical aspects of NDA submission.
25 March 97	ROC	F. Longenecker contacted M. Johnston (CSO, FDA) regarding minutes of 1/23/97 meeting. F. Longenecker noted that VII3 and 4 and VIII 1 were unclear or disagreed with NNPI minutes. Also discussed was E-mail connection between NNPI and FDA.
4/24/97	100	IND Safety Report - second follow-up report RE: Mfr. Cont. No.: 95/1844. New information in Item B.5, C.2 and C.3 and C.4. The investigator considers the causality of the event "carcinoma colon, ileus, cardiac failure" as possible, stating, "...we all know that there is nothing in medicine which is not possible." The sponsor considers the event unlikely related. (xref: Initial report, Serial No. 048 submitted 7/1/995; 1st follow-up, Serial No. 094, 12/19/96).
4/29/97	**101**	Protocol Amendment- revised investigator information **for principal investigator,** Dr. Arthur Green, DO, Study # AGEE/DCD/065/USA. Changes to Items 1,3,4,5,& 6 on Form 1572.
6/25/97	ROC	FRL contacted M. Johnston to inform him that NN would submit the NDA for repaglinide within a week. The NDA was in 453 volumes and would be shipped from Denmark withina week. FRL also asked M. Johnston where the field copies should be sent. M. Johnston called back and said that the field copies should be sent to NJ district office located in Parsippany.
6/26/97	ROC E-Mail	M. Johnston requesting a desk copy of the following from the NDA: TOC, Cover letter, Patent information, debarment information, ISE and ISS. Since the ISE and ISS alone would be over 10 volumes, it was agreed that only the text portion of the ISE and ISS would be sent in a week or two. M. Johnston also requested he should be copied on the cover letter only for any future submissions.
7/16/97	102	Annual Progress Report for time period March 1, 1996 through February 29, 1997.
12/22/97	103	Submission of original protocol AGEE/DCD/081/USA titled "A Randomized Study of Repaglinide and Troglitazone in Treatment of Type II Diabetes in combination and individually, using both a fixed dose and a titration to maximal effect".

NNPI OFFICIAL INFORMATION CHRONOLOGY

AG-EE 623 ZW Tablets (oral hypoglycemic agent)

IND 39,012

01/26/98	104	Revised protocol AGEE/DCD/081/USA. This revised final version is dated 1/9/98 and is titled "Revised Final, Version 1".

H:\INDLOG\AGEE623

6

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
6-25-97	ROC	Fred Longenecker (FRL), Manager, Regulatory Affairs of NNPI telephoned Michael Johnston, Consumer Safety Officer of FDA to inform that Novo Nordisk would be submitting the NDA for repaglinide tablets within a week. There were 453 volumes of the NDA and they would be shipped from Denmark.in approximately 75 boxes.
6-26-97	ROC	M. Johnston requested a desk copy of several parts of NDA 20-741. He noted that he wanted to get DSI audit settled early and a Dr. Tom Ju of FDA would call shortly for information needed to get the audit underway. M. Johnston would be the source contact for FRL and that he would use the e-mail as a means of communication.
6-27-97	ROC	(FRL) telephoned Michael Johnston of FDA to find out where to send the user fee check for the NDA. He was told to call Mr. Thomas Hassall of the User Fee Staff. Mr. Hassall stated that the user fee was $205,000 half of which ($102,500) should be sent at the time of filing along with a user fee cover sheet. A copy of the same should be faxed to the reviewing division and the central document room who would be assigning a user fee id# as the volumes were being shipped from NNAS.
6-30-97	ROC Fax Memo Fax	FRL called Michelle Hall of FDA (central document room) who assigned a user fee id# 3283. Since the document room did not have a telefax, she requested that the original user fee cover sheet be mailed to her. FRL said that it would be sent via fed-ex. Assignment of user fee id #3283 faxed with a note that the number should be noted on the submission and the payment. FRL to Michelle Hall stating that the user fee cover sheet, letter to Dr. Sobel and FDA 356h were sent via fed-ex. FRL to M. Johnston: copy of user fee cover sheet, cover letter and 356h that was mailed to Dr. Sobel.
7-08-97	Letter	FDA acknowledging the application of Prandin© (repaglinide) tablets, 0.5 mg, 1 mg, and 2 mg. The reference number is NDA 20-741 with a filing date of June 27, 1997and receipt date of 07-01-97. The letter also stated that unless FDA notifies NNPI within 60 days of receipt date that the application is not sufficiently complete to permit a substantive review, the application will be filed under section 505 (b) of the Act on August 31, 1997 in accordance with 21 CFR 314.101 (a). The letter further stated that NNPI could request an informal conference with DMEDP (to be held in 90 days) for a brief report on the status of the review of the application.
7-10-97	Letter and Desk Copy	The following items were sent in 4 volumes to Mike Johnston (CSO) of FDA as his desk copy: Vol. 1 consisting of cover letter, confidentiality & debarment statement, GCP statement, reviewer's guide, field copy certification, overall NDA index, patent info., vol. 2 had draft labeling with package insert and container & carton labels, vol. 3 was ISE with text and in-text tables, vol. 4 was ISS with text and in-text tables.
7-11-97	ROC	Call from Dr. Ju of FDA regarding FDA plans for auditing repaglinide clinical studies. Dr. Ju requested a list of studies and sites in US and Europe to audit and to do that he would need a listing of protocol names and numbers, a list of names and addresses of investigators for each study and the number of patients enrolled and the number completed, a copy of the application summary of all sections.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
7-16-97	Fax	FRL to Michael Fossler and Ting Ong responding to their inquiry about the composition of McIlvaine's buffer (pH 5.0) used in the dissolution test for Prandin tablets. FRL replied that the buffer is prepared by dissolving 10.30g. citric acid monohydrate and 18.16g. disodium dihydrogen phosphate dihydrate in water to a final volume of 1 liter.
7-18-97	Letter	Copies of the following sent to Dr. Ju that would provide information prior to initiating audits of clincal trials presented in the NDA: Tables of all nine adequate and well-controlled repaglinide clinical trials, alphabetical listing (by trial) of investigator and trial site, listing by investigator of the number of patients enrolled and the number that completed the study at that site, copy of application summary of original NDA.
7-21-97	Fax ROC	M. Johnston to FRL requesting submission of all PK/PD data on behalf of Michael Fossler from studies 055/UK, 007/D and 064/USA in ASCII or Excel spreadsheet form and any study data that might be helpful in the review. Also a study synopses for all clinical pharmacology studies be submitted in WP 6.1 if possible. M. Johnston called FRL to state that the initial review of the NDA was going well and gave names of following reviewers: Medical - John Gueriguian, M.D., Biopharmaceutics - Michael Fossler, Ph.D., Statistics - Daniel Marcello, Ph.D., Nonclinial Pharmacalogy - Herman Rhee, Ph.D., Chemistry - Xavier Ysern, Ph.D., Environmental Assessment - Nancy Sager, Ph.D. FRL called Dr. Fossler to see if the synopses of clinical pharmacology could be sent in MS Word as switching to WP 6.1 caused some difficulties. Dr. Fossler agreed.
7-22-97	Fax ROC	In response to Dr. Ju's request, FRL sent the titles for study 033, 049 and 064. Call from Dr. Ju regarding the information sent to him to plan audits of clinical studies. Dr. Ju had a few questions on the studies, type of study, dose range in labeling and if the three US studies covered all aspects of labeling and if studies in Europe and Australia duplicated this work. FRL provided answers to all his questions.
7-29-97	ROC	Dr. Ju with Madhavi Prakash requesting the following documents for clinical audit of sites 033, 049 and 064: Form 1572, original protocols and amendments with dates, total number of patients who entered the study, number of dropouts, protocol violators, individual listing of AE and completed CRF for specific patients.
8-01-97	Submission	Information requested by Dr. Ju on study sites 033, 049 and 064 in USA for clinical trial audits. The submission had the following for each site: copy of form 1572 for the study investigator, original protocol, amendments with dates, patient completion status, total number of patients who dropped out, reason for dropout, identification of patients who were protocol violator, listing by patient of individual AE, completed CRF's.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN® (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
8-06-97	ROC Memo	Dr. Rhee of FDA called Maryann McElligott to speak to the toxicologist/pharmacologist to determine: how the AUC of repaglinide animal/human was calculated and if it included parent metabolites. He questioned it because the metabolites in dog/rat and human are so different. He indicated that he needed a quick response for a cancer assessment meeting. B. Reit to B. Poole giving a summary of issues regarding FDA's request for NN to consider requesting a priority review for repaglinide as: Dr. Guerigian (MedicalReviewer, FDA) called and indicated that based on the proposed product profileit appears that repaglinide may be a unique OHA
8-08-97	Letter	B. Reit to M. Johnston requesting that the Prandin NDA be granted priority review status by the FDA with NN making the following commitments: requested data sets to be sent to FDA in 2 weeks, discussion of AUC data with Dr. Rhee accomplished, NN will be prepared for the ACM meeting in November and that NN is committed to market Prandin soon after approval.
8-11-97	E-Mail Fax	M. Johnston to FRL stating that the new Environmental Assessment regulation will allow this NDA to be covered under a categorical exclusion, therefore Novo Nordisk should request the withdrawal of the environmental assessment and replace with a request for categorical exclusion. FRL sent information to Dr. Herman Rhee of FDA with response to requests made by FDA during a teleconference discussion of 8/7/97 between Dr. Rhee and NNPI and Dr. Karl Thomae GmbH. The following was included: Comparative metabolic profile, dose levels in the carcinogenicity studies, historical control - rat liver tumours
8-13-97	Fax	FRL sent additional summary clinical information on repaglinide as requested by M. Johnston and Dr. Guerguian for review prior to internal agency meeting.
8-14-97	Letter with Amendment 1	Amendment sent to FDA to withdraw the environmental assessment submitted in the original NDA 20-741 (volume 1.008, pages 293 to 316), and requesting a categorical exclusion from submitting an environmental assessment as allowed under 21 CFR 25.31 (b).
8-15-97	ROC Fax	M. Johnston called FRL stating that the NDA was accepted for expedited review by the division and that NN should begin preparing an advisory committee package. Included in the package should be protocols for two phase IV studies. He also stated that Kathleen Reedy, executive secretary for the ACM would be working closely with NN. Corrected version of additional summary clinical information on repaglinide was sent as the one sent on 8/13/97 was found to have inaccuracies on three pages which were since corrected.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
8-19-97	ROC	FRL contacted M. Johnston about the Phase IV plans and safety update. M. Johnston stated that FRL should call Dr. Fleming directly to discuss the phase IV requirement as it relates to the development of the protocol. FRL stated that the study report and data set for 065/USA was nearing completion and would be sent in early September.
8-20-97	Letter and Amendment 2	Submission of SAS data sets from the working data base for the following US studies: 033, 049 and 064. 2nd SAS data sets from the original data base for the following studies: 033, 064, 049 (all US studies), 046 (UK), 047 (F-B-I), 048 (DK-N-S-SF, 050 (NL-D), 028 (NL), 053 (AUS).
8-25-97	ROC ROC	FRL contacted Dr. Herman Rhee to discuss the status of HPB clinical hold on repaglinide. Dr. Rhee had questions on carcinogenicity studies and discussed issues of limb deformation in rat reproduction toxicology studies and body weight correlation. FRL received a call from Kathleen Reedy, Executive Secretary for ACM stating that the meeting was tentatively scheduled for November 19, 1997 and that NN should send 30 copies of the briefing document for the committee by 10/27. She gave some names of committee members and 5 standard questions that would be asked by the comittee.
8-26-97	Fax Letter and Amendment 3	FRL sent background information and discussion questions for Dr. Fleming's review prior to the scheduled conference call for August 27, 1997. Submission of data sets in ASCII format of Pharmacokinetic/Pharmacodynamic data from studies 007/D, 055/UK and 064/USA for Dr. Fossler.
8-27-97	ROC Amendment 4	Teleconference with Dr. Fleming and M. Johnston regarding Phase IV studies and NDA review logistics. FRL, BREI, JOWH participated in the call. Submission of electronic copies of various study reports/synopses in MS Word 7.0 format. A full set of disk was submitted for archives and individual set each for Dr. Fossler, Biopharmaceutics reviewer (synopses of 27 clinical pharmacology studies), Dr. Fleming and Dr. Gueriguian, Clinical reviewers (synopses of 39 clinical studies), Dr. Taneja (9 studies supporting safety and efficacy).

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
09-02-97	Letter and Amendment 5	Submission of answers to Dr. Herman Rhee who had 3 questions on Carcinogencity and Reproduction Toxicology studies. The questions were based on the calculation of plasma levels at 8 am & 4 pm, whether the levels were free rather than bound drug, and the cause of limb deformation in rat reproduction studies and data that supports it.
09-05-97	ROC	Kathleen Reedy with FRL stating that the official ACM meeting would be held on November 19 at the Holiday Inn - Bethesda, MD. She had questions on the NDA, generic and trade name of the product to note in the official document.
09-08-97	Letter and Amendment 6	Submission to FDA requesting that the trade names Prandin™ and Actulin™ both be submitted to the trade mark committee for review to determine whether they will be acceptable names for repaglinde tablets marketed in the US.
9-09-97	ROC	Ms. Kathleen Reedy of FDA called FRL with additional information on the ACM meeting and wanted to know the information that goes into the FR notice. She indicated that she would be away in October and would like to get the arrangements for the meeting underway before she leaves.
9-10-97	ROC	FRL with Melissa Egas , Pat Elliot and David L. Duncan of FDA regarding PAI of Sipsy from October 8-10 by Gwyn Dickinson, Inspector. FRL then contacted M. Johnston to request that any future contacts be made through NNPI. FRL further contacted Ms. Egas (she was out, so he spoke to Patricia Elliot) to see if Sanofi site would be inspected.
9-11-97	ROC	David L.. Duncan of FDA called FRL stating that Unipack sites from October 27-31 in Bolton and Shotgate, England would be inspected and wanted to know what operations they performed for repaglinide tablets. He requested the assistance of NN in setting up the inspection. FRL stated that he would have the company make the hotel reservations and any other assistance he might need for the inspection.
9-11-97	ROC	FRL called Kathleen Reedy to inform her that she could go ahead and make the ACM notice public (after FRL verified by STJA). Ms. Reedy said that the notice was sent to FR and she would add it to the hotline for public access. She also said that the venue for the meeting had changed from Holiday Inn, Bethesda to Ramada Inn, Bethesda and that she would reserve a section for 30-40 attendees from NNPI.
9-16-97	Fax Fax	FRL sent additional copies of the draft protocol outlines that was originally sent on 8/26/97 to M. Johnston who could forward them to cardio-renal for a consult. FRL sent a copy of a letter to Nicholas Nemery of NNAS. The letter was from David Duncan of FDA confirming inspection of Unipack Ltd., in Shotgare and Essex in UK on 10/27-28 and Westhaughton, UK on 10/30-31.
9-17-97	Letter and Amendment 7	Results of new evaluated data to determine the reanalysis of plasma repaglinide (requested by M. Johnston on behalf of Dr. Fossler) in comparison to the initial analysis data in the original study report for study 040/USA. Result of comparison showed while there changes in the raw data and derived parameters based upon the reanalysis they do not alter the conclusions of the original study report.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN® (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
9-18-97	Fax E-Mail	FRL to Deborah Browning of FDA with details of transportation and lodging for Robert Horan, Inspector who was going to inspect the Unipack sites. M. Johnston sent update on following: proposal for amendment 8 is fine with Dr. Gureiguian, trade names Prandin™ and Actulin™ were sent to Nomenclature committee for review after Dr. Ysern's review, consultation with cardio-renal division to be sent out upon Dr. Fleming's return to office.
9-24-97	E-Mail	FRL requesting M. Johnston's assistance and input to submit an amendment for approval of an aluminum foil blister package for samples only. The amendemnt would include: information about the components of the blister package, protocol and report of 9 months stability data, stability commitment and draft labeling for blister carton samples.
9-26-97	E-Mail	FRL to M. Johnston requesting the status of the CAC evaluation of repaglinide .
9-29-97	E-Mail	FRL to M. Johnston requesting Dr. Ysern's opinion regarding a unique id system for solid oral dosing forms. NN's id system for repaglinide tablets only would have "Apis" bull (trademark for NN) imprinted on the face of the tablet and a color coding for each strength. FRL also wanted clarification on geriatric testing of bottles (he was under the impression that it would be the agency requirement in 1998) since the NDA was filed in 1997. M. Johnston replied that he consulted with the two chemistry team leaders and neither were aware of this requirement in 1998. He thought that it could be a Consumer Product Safety Commission requirement and wanted FRL to send him the reference along with a new label with the "geriatric use" section added. FRL replied that he was trying to clarify the information about the geriatric testing of bottles and that geriatric labeling would be included in the revised package insert based upon the safety update that would be submitted mid-october.
9-30-97	E-Mail	FRL to M. Johnston with an alternate proposal to the blister sample for Dr. Ysern's input. The proposal would use a sample container which uses the existing 15ml HDPE (DUMA) bottle used to package 100 tablets but containing 30 tablets & the empty space would be filled with cotton. A new labeling would be submitted with a stability commitment.
9-30-97	ROC	Dr. Herman Rhee contacted FRL with questions on the rat carcinogenicity study (46Q) for CAC review. The questions were: (1) Do the data in the tables presented in NDA volume 1.024 represent body weight gain difference or absolute body weight difference? (2) Were the two control groups in the study treated any differently in terms of how they were dosed? (3) Explanation for the big difference between body weight gain for the two control groups (4) Where did the clinical AUC value which was used to calculate the AUC ratios come from? FRL stated to Dr. Rhee that NN would respond to his questions shortly. FRL requested MAK to have Thomae develop answers to Dr. Rhee's questions and also requested Dr. Fred Reno for his input. Dr. Fossler called FRL regarding the third generation assay validation assay report 940387 and if NN could provide spike concentrations for samples K1 through K6 presented in table 4 (NDA volume 1.053). FRL stated that he would contact NNAS and respond with an answer.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN® (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
10-01-97	E-Mail	FRL responsed to question from Dr. Fossler regarding spike concentrations as follows: The control samples were prepared separately via dilution from a stock repaglinide solution of 1035 ng/ml: K1 - .9ng/ml, K2 - 1.8 ng/ml, K3 - 5.0 ng/ml, K4 - 25 ng/ml, K5 - 56 ng/ml and K6 - 110 ng/ml.
10-02-97	E-Mail	Response from Mike Johnston, CSO of FDA to FRL's questions on CAC date, Biopharm requests, Nomenclature committee, senior bottle testing, tablet ID system, proposed blister pack packaging, proposed 30 tablet bottle, and labeling.
10-03-97	E-Mail ROC Letter and Amendment 8	Status to Mike Johnston of FDA regarding Amendment 008, documentation for amendment to sample packaging in preparation by NNAS, labeling change with the safety update, and safety update. Karen Somers of FDA sent telephone number for Hearings-on-the-line which provides telephone narrowcasts (202) 966-2211 and FDC Reports 1-800-332-2181 which provides videotapes of all FDA open meetings. ROC initiated by Dr. Michael Fossler of FDA regarding manufacture of dissolution batches of repaglinide tablets. Dr. Fossler was calling to clarify the manufacturing sites that were used for repaglinide tablets. Amendment No. 8 for Clinical Safety Study AGEE/DCD/065/USA. The submissioin included the Integrated study report, SAS data sets and supporting files and information, Electronic copies of the study synopsis in MS Word.
10-06-97	E-Mail	Initial response by FRL to Dr. Fossler with copy to Mike Johnston regarding Biopharm request for variability analyses and t [illegible] analysis from Study 064. FRL responded that the requested analyses were not conducted but that it was being done now. He expected to send another response within two days.
10-07-97	E-Mail	FRL sent a description to Dr. Mike Fossler with copy to Mike Johnston of the methodology used to calculate inter and intra-patient variability for study 064/USA as an attachment in MS Word.
10-08-97	Fax ROC Fax	FRL sent the tables of Cmax and tmax values for the three meal-related doses for each dose group at the four weekly testing points in study 064/USA. This information was requested by Dr. Mike Fossler of FDA. FRL responded to a telephone message from Dr. Herman Rhee of FDA concnerning the status of responses to questions on rat carcinogenicity study 46Q. FRL faxed information to Dr. Herman Rhee responding to his request made during a teleconference of September 30, 1997.
10-09-97	E-Mail	Response by FRL to Dr. Mike Fossler with copy to Mike Johnston regarding biopharm question on process/equipment comparison. A copy of the document showing the comparison of the manufacturing process and equipment for tablets used in bioequivalence study 070/USA was sent via fax.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
10-10-97	E-Mail	Response from Mike Johnston to FRL on the weekly update for the week of 10/9/97. M. Johnston appreciated the timely response to FDA reviewers especially biopharm and pharmacology.
10-14-97	Letter and Amendment 9	Amendment No. 009 dated consisting of safety update document/ revised package insert with/ without annotations was sent to FDA.
10-16-97	Letter and Amendment 10	Amendment No. 010 submitted for packaging of physician samples of each tablet strength, use of trade name Prandin© for repaglinide tablets marketed in the US, support for tablet id system proposed in original NDA, removal of Sanofi (Highland) Pharmaceuticals, Inc. from NDA 20-741, Unipack to handle all packaging of repaglinide tablets at its two facilities.
10-17-97	E-Mail	Status update sent by FRL to M. Johnston for the week of 10/13/97.
10-20-97	ROC	FRL called Dr. Rhee to inquire about the results of the CAC meeting held the previous week. Dr. Rhee stated there were issues that NN needed to resolve based on analysis of tumor data by the statistician. He had other questions on the study and FRL replied that he would get back to him with answers.
10-22-97	Telephone	FRL, BREI, JOWH and WCH called Dr. Fleming requesting an opportunity to discuss presentation of hypoglycemia and cardiovascular events in the ACM briefing document and at the meeting on November 19, 1997. Dr. Fleming stated that these issues should be discussed in a teleconference on 10/23/97.
10-23-97	Teleconference	FRL, BREI, JOWH and WCH with Dr. Fleming discussed issues for the upcoming ACM meeting and what Dr. Fleming would need prior to the meeting.
	Fax	FRL sent Dr. Rhee responses to his questions of 10/20/97.
	E-Mail	FRL to Mike providing update for the week of 10/23/97.
	Letter and Amendment 011	Responses to questions on preclinical and biopharmaceutics review and requests for clinical information.
10-24-97	Fax	M. Johnston to FRL with general and labeling comments from completed Biopharmaceutics Review conducted by Dr. Fossler.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN® (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
10-30-97	E-Mail	M. Johnston to FRL acknowledging receipt of amendment 011 and he requested that if FRL got the labeling comments it should be reviewed. FRL wrote back that the comments were received and NN was developing the responses.
	E-Mail	BREI to FRL stating that Dr. John Guerigian from FDA had called him to state that he had completed his review and has high opinion about repaglinide. He also wanted to meet and discuss some triple combination studies for diabetics and things to improve frequency of hypoglycemic events. He would like to meet in early December.
	ROC	Dr. Rhee called FRL to inquire about the rat reproductionstudies referring to segment III study 96Q and the limb deformation seen in pups. FRL answered his inquiries.
11-06-97	Fax	M. Johnston sent fax to FRL that included acceptable chemical structures and a draft of comments by Medical Review.
	E-Mail	Update from M. Johnston to FRL for week ending 11/6/97. Update included medication guides, labeling, review status by biopharm, medical, chemistry, DSI Audits, establishment evaluation, statistical review and pharmacology.
11-07-97	E-Mail	M. Johnston asking FRL if NN requested exclusivity in the NDA submission and FRL replied that he did not believe NN specifically requested exclusivity. Dr. Fleming asked FRL if there was any specific analyses of EKGs and if QT interval was measured and tabulated. He requested to speak to Dr. Faisch the following week. FRL replied that EKG data would be faxed shortly and Dr. Faisch & John Whisnant would call directly.
	Fax	M. Johnston sent Pharmacology labeling changes to FRL.
11-10-97	Fax	FRL to Dr. Fleming with information for an upcoming teleconference. There overview of tables (in Powerpoint) of ECG data requested by Dr. Fleming. The tables provide PR and Qtw data for key US studies and a comparison of the frequency of significant changes.
11-11-97	Fax	FRL to Dr. Fleming with information for the teleconference. There were copies of overheads prepared for the ACM and these would be used as the basis of a discussion about post-marketing study of CV safety.
11-12-97	ROC	FRL with Dr. Fleming. Summary of teleconference between Barry Reit, John Whisnant, FRL of NNPI and Dr. Fleming of FDA includes discussion of the upcoming ACM meeting and any requirements of data by FDA to be provided prior to the meeting.
	Fax	Dr. Fleming requested that NNPI provide a copy of the phase IV protocol slides to Dr. Maryann Gordon (cardio-renal consultant) for review. The copy was sent by fax to Dr. Gordon by FRL.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN® (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
11-11-97	Fax	FRL to Dr. Fleming with information for the teleconference. There were copies of overheads prepared for the ACM and these would be used as the basis of a discussion about post-marketing study of CV safety.
11-12-97	ROC	FRL with Dr. Fleming. Summary of teleconference between Barry Reit, John Whisnant, FRL of NNPI and Dr. Fleming of FDA includes discussion of the upcoming ACM meeting and any requirements of data by FDA to be provided prior to the meeting.
	Fax	Dr. Fleming requested that NNPI provide a copy of the phase IV protocol slides to Dr. Maryann Gordon (cardio-renal consultant) for review. The copy was sent by fax to Dr. Gordon by FRL.
11-13-97	Fax	Draft of revised package insert with NNPI comments on items that NNPI disagreed with and some that NNPI agreed with if modified, were sent to M. Johnston by FRL.
	ROC	Initiated by FDA. Telephone call between Dr. Gordon, Dr. K. Mahjoob of FDA and AHB, FRL regarding phase IV CV safety trial.
	E-Mail	FRL to M. Johnston about the status of the labeling with proposed modification sent to FDA. FRL also asked about marketing's proposal to add a logo to the sample labels and cartons.
11-14-97	E-Mail	M. Johnston to FRL stating that the labeling was easy to understand, it was okay to print the carton labels and that NNPI should send the new carton labels with the logo for Dr. Ysern of FDA to look over.
	Fax	FRL faxed copies of carton labels with four proposed logos to be used in place of the trade name for Dr. Ysern to look over. Fax from Dr. Maryann Gordon with comments by Dr. Mahjoob sent to FRL recommending that a lot of planning and discussion take place prior to finalizing phase IV study.
11-17-97	Fax	FRL to Dr. Herman Rhee with response to question from CAC. Response contained pages from NDA volume 037 showing the thyroid function results from study 067S.
11-21-97	E-Mail	Dr. Fleming to FRL congratulating on a successful ACM meeting. He requested that NNPI send a description of all thestudies and other actions that was going to be done as a response to the concerns by the committee. They would then put them in the approval letter. FRL to Dr. Fleming. Conveying his appreciation of support at the ACM meeting. A draft of the text for the approval letter was included in the e-mail.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
11-24-97	E-Mail	Draft of following documents were sent to Dr. Fleming per his request: (1) MS Word draft of PI dated 11/12/97 (2) MS Word document of NNPI responses to FDA labeling comments (3) Bar graphs in Powerpoint from the ACM showing ending doses in the AC trials.
	ROC	FRL and Dr. Fleming regarding a teleconference. NNPI made commitments that would go in the approval letter.
11-25-97	Fax	FRL received a copy of the Executive CAC report reflecting a briref summary of the committee discussion and its recommendations. Ron Steigerwalt of FDA sent the report with his statement on the cover page.
11-25-97	Fax	FRL received a copy of the Executive CAC report reflecting a briref summary of the committee discussion and its recommendations. Ron Steigerwalt of FDA sent the report with his statement on the cover page.
12-02-97	E-Mail	Suggested changes to package insert by Dr. Fleming with DDMAC's suggestions incorporated into it sent via e-mail attachment
12-03-97	Fax	Marianne Kock of NNAS sent a fax to FRL from Thomae with two questions dealing with bio-batches that were mentioned in the CMC part of the NDA and what was Novo's definition of bio batches.
	Fax	Labeling revisions to the nonclinical section of the draft package insert sent by FRL in response to a request by Dr. Steigerwalt.
	ROC	Discussion with Dr. Fleming re: package Insert - UGDP warning. It is summarised that it is too soon to remove the UGDP warning from OHA labeling. More data, a separate ACM and time are needed. FDA is open to NNPI participation in bringing the issue to a public forum.
12-04-97	E-Mail	M. Johnston to FRL with update. Pharmacology review done, all DSI audits are back, phase 4 language seems okay, he is still looking for final draft label once completed with Dr. Fleming, a new debarment statement.
12-05-97	Fax	Revised debarment statement as requested by M. Johnston. Copy of the mock-up for the sample carton for M. Johnston and Dr. Ysern's review.
	E-Mail	FRL to Dr. Fleming. Revised draft package insert in two versions (marked and unmarked) for his review. Document explaining what changes have been made and why. Document with tables and figures supporting the revisions made. AE's from placebo control and 1 year studies.
	ROC	FRL with Dr. Steigerwalt stating that Dr. DeGeorge of the CAC had disallowed most of Dr. Lehmann's (consultant) alternate wording.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
12-09-97	E-Mail	FRL to M. Johnston re: launch materials. Marketing wanted to get DDMAC approval on some pre-launch materials and wanted to send two single "teaser" page institutional ads for review to DDMAC along with a draft of PI currently under review. The core launch materials are being developed and will be ready to send out for review in January.
12-11-97	Letter	Pre-launch institutional advertisements (items 123585A & 123585B) along with a a copy of the current draft PI currently under final review sent to Mark Askin of DDMAC in FDA.
	E-Mail	FRL to Dr. Fleming requesting a tele-conference to discuss clarification of several comments made in the PI. Attached were 5 ISS tables relating to an item on page 11 of PI.
12-12-97	E-Mail	Final draft package insert (dated 12/12/97) sent as an attachment to Dr. Fleming to present to Dr. Bilstad.
	Letter and Amendment 12	Following pre-approval items were included in this amendment: signed version of the revised debarment statement as requested by M. Johnston, final PI revised per discussion with Dr. Fleming for submission to Dr. Bilstad.
12-15-97	E-Mail	M. Johnston to FRL with update. Labeling being reviewed by Dr. Bilstad and Ms. Lee Ripper (assistant to Dr. Bilstad). Phase 4 wording was put into letter. FDA still waiting on several of the "Establishment Evaluation Requests" to be returned with an acceptable status. Dr. Sobel to get the "Package" for review. Labeling meeting scheduled for Wednesday, 12/17/97. Dr. Fleming to FRL stating that the labeling looks OK except for a minor change "Accordingly, initial dosage adjustment does not appear to be necessary, but subsequent increases in PRANDIN should be made carefully in patients with type 2 diabetes who have renal function impairment or renal failure requiring hemodialysis."
12-17-97	E-Mail	M. Johnston to FRL requesting a letter listing the phase 4 commitments.
	Letter and Amendment 13	Letter detailing phase IV commitments sent via fax and overnight mail as requested by M. Johnston.

NNPI OFFICIAL INFORMATION CHRONOLOGY

NDA 20-741

PRANDIN® (repaglinide) tablets
Approval Date: December 22, 1997

DATE	CONTACT TYPE	DESCRIPTION
12-18-97	E-Mail	M. Johnston to FRL stating that the resubmitted debarment statement of 12/5/97 not OK. Statement was reworded in the e-mail with a request that a changed version be faxed ASAP.
	Fax	FRL to M. Johnston re: PI. Upon re-reviewing the draft NNPI came across several small changes that needed to be made for the final version. FRL detailed the changes in the e-mail and faxed it to M. Johnston.
	Telephone Call	M. Johnston to FRL stating that Dr. DeGeorge had requested additional revisions to the PI. These changes were detailed in the e-mail. All final paperwork including the PAI reports were recevied by him. PI discussion was the last item to resolve before they could send an approval letter.
	Letter and Amendment 14	Revised signed debarment statement sent via fax and overnight mail.
12-19-97	Fax	FRL to Dr. James Bilstad and M. Johnston re: PI revisions. Revisions were made to the paragraph on renal insufficiency on page 10, hypoglycemic event information on page 22, two separate revised versions of the AE table on page 23 and CV events table on page 24.
12-22-97	Fax	2 sets of Package insert revisions made after earlier discussion in the day sent to M. Johnston.
	Amendment 15	Phase IV commitments made by NN for post-marketing clinical trials. Commitments were made for: (1) a long term simplified clinical trial to assess further the long term safety including incidence of CV events in patients with type 2 diabetes treated with Prandin, a long-acting sulfonylurea drug, and other established therapy, (2) efficacy in patients with type 2 diabetes and renal dysfunction, (3) normal volunteer studies to document pharmacokinetic interaction with statins, estrogen and calcium channel blocker.
	Fax	**Approval letter** from FDA to Dr. Reit stating that the NDA dated June 27, 1997 and all the amendments associated with the NDA were received. It further stated that the FDA had completed the review of the application as amended and had concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling and therefore the application is **approved effective December 22, 1997.**